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CONTENTS

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PRIMARY TUBERCULOUS INFECTION IN CHILDHOOD

INCIDENCE, MORBIDITY, AND MORTALITY IN AN URBAN POPULATION

BY

BRIAN C. THOMPSON, M.D.

(From the Ealing Chest Clinic, London)

It is universally recognized that tuberculin skin tests done on a mass scale can afford epidemiological information of great value in an anti-tuberculosis campaign. In many countries extensive and repeated surveys have been made during the past twenty-five years in various population samples. It has been conclusively shown, for instance (Myers, 1944), that in the United States tuberculous infection has become measurably less frequent and has become postponed to a later age—this change taking place to a degree greater in some communities than in others. In Great Britain, no comparable studies are available. Tuberculin testing of children has been limited to hospital patients (Schlesinger and Hart, 1930; Dow and Lloyd, 1931; Bradshaw, 1939); and the only large-scale work on unselected children is that of Jones Davies (1943) in a Welsh rural area, and of Heimann and Paterson (1945) in Bournemouth.

Tuberculin Sensitivity

During the years 1942–45, inclusive, 1,476 children below the age of 14 made an initial attendance at the Ealing Chest Clinic. Of these, 1,050 came primarily without symptoms, as contacts of known cases of tuberculosis. The remaining 426 were referred by general medical practitioners or medical officers to the school or infant welfare clinics on account of specific symptoms. The former 1,050 we designated 'contacts,' the latter 426 'non-contacts.'

Our routine technique of tuberculin testing was as follows. A visiting nurse applied a tuberculin patch (Vollmer type) at the patient's home three days before his appointment at the clinic, with instructions for it to be removed forty-eight hours later. The test was read at the time of attendance, and, if negative, was followed by an intradermal (Mantoux) injection of ·01 c.cm. of tuberculin-purified protein derivative, second strength, or of 1/100 old tuberculin during a period when the former was unobtainable. That such a relatively strong dose was justified is shown by the high percentage of positive reactors it revealed in children negative to the patch test. At the same time, the almost complete absence of severe reactions from the intradermal test has satisfied us that the tuberculin patch as used at Ealing, contrary to the experience of some others (Deane, 1946), is in general a reliable index of tuberculin sensitivity when this is relatively high.

The 'complete' tuberculin test was attempted in most contact children over the age of one year, and usually in non-contacts when a second attendance could be obtained. Patients not infrequently failed to return for reading of the intradermal test, and sometimes flatly refused to submit to the injection, so that we were left with a record of the patch result only. In spite of this, nearly half of both contacts and non-contacts negative to a patch test subsequently underwent a satisfactory intradermal test. On the perhaps unjustified assumption that these were more likely than not to be positive, we tended to omit altogether tuberculin testing of the older age groups. Such children were x-rayed in the first instance, but in younger children only those tuberculin-positive were x-rayed. The comparative figures are seen in columns 2 and 3 of table 1.

The 1,050 contacts were distributed fairly evenly by age; of the 426 non-contacts, relatively few were infants, because outside practitioners tended not to refer very young children to the clinic. The number of children patch-tested at each year of age, and the number patch-negative who were subsequently Mantoux-tested, is shown in columns 3 and 6. Column 5 shows the patch-sensitivity rates. In order to compute the complete test-sensitivity rates, the observed percentage of Mantoux reactors must be applied to the total patch-negative, as if all patch-negative children, instead of only a sample, had undergone a Mantoux test. This operation gives the adjusted figures shown in column 9. For example, 8·9 of every 100 contacts below the age of one were patch-positive. Of the remaining 91·1, 30 per cent. were Mantoux-positive, that is, 27·3. Thus the total percentage reacting

TABLE 1
TUBERCULIN SENSITIVITY IN 1,476 CHILDREN

Age in years	Total children	Patch Test			Mantoux Test 1 : 100				Complete Test
		Total	No. positive	Per cent. positive	Total	No. positive	Per cent. positive	Per cent. positive (adjusted)	Per cent. positive (10) [(5)+(9)]
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
				Contacts					
0	92	90	8	8·9	10	3	30·0	27·3	36·2
1	80	78	15	19·3	27	15	55·6	44·8	64·1
2	68	67	17	25·4	21	12	57·1	43·2	68·6
3	82	79	20	25·3	28	15	53·5	41·7	65·7
4	73	69	22	31·9	22	12	54·5	38·0	69·9
5	84	80	32	40·0	24	17	70·8	42·5	82·5
6	77	73	22	30·1	26	10	38·9	27·2	57·3
7	74	70	30	42·9	22	8	36·4	20·7	63·6
8	70	64	26	40·6	21	9	42·9	25·5	66·1
9	76	71	29	40·8	29	15	51·7	30·6	71·4
10	55	47	17	36·2	14	9	64·3	41·0	77·2
11	73	58	19	32·8	22	11	50·0	33·6	66·4
12	79	38	16	42·1	13	6	46·2	26·7	68·8
13	67	10	3	30·0	3	2	66·7	46·7	76·7
Total	1,050	894	276	30·9	282	144	51·1	35·3	66·2
				Non-Contacts					
0	2	2	1	50·0	0	0	0·0	0·0	50·0
1	8	8	0	0·0	1	0	0·0	0·0	0·0
2	14	11	2	18·2	2	1	50·0	40·9	59·1
3	22	17	3	17·6	6	2	33·3	24·4	42·0
4	21	18	0	0·0	12	2	16·7	16·7	16·7
5	51	47	6	12·8	18	3	16·7	13·2	26·0
6	60	50	5	10·0	18	8	44·4	39·9	49·9
7	37	30	7	23·3	11	6	54·5	41·8	65·1
8	40	32	6	18·7	9	4	44·4	37·7	56·4
9	37	28	4	14·3	14	7	50·0	42·8	57·1
10	24	18	3	16·7	8	4	50·0	41·7	58·4
11	32	22	4	18·2	11	7	63·6	52·0	70·2
12	36	11	2	18·2	3	2	66·7	54·5	72·7
13	42	14	6	42·8	4	1	25·0	14·3	67·1
Total	426	308	49	15·9	117	47	40·1	33·7	49·6

to tuberculin in this age group is 8·9 plus 27·3=36·2, as shown in column 10.

In the case of contact children, it is clear that a degree of saturation is reached at an early age, after which the proportion of reactors increases but little with each year of age. This is demonstrated histographically in fig. 1, which also shows that much lower figures would have resulted from using the patch test alone.

The total non-contact children, and the proportions tuberculin-tested, were too small to be treated in single year-groups. In fig. 2 they are collected in larger age periods and compared with contact children. The steep rise of positive reactivity in non-contacts is well marked, and again the superiority of the complete test over the patch test is clearly demonstrated.

Tuberculin sensitivity in non-contacts is, as might be expected, less than in contacts at all ages; but it increases much more rapidly with age, to become nearly equal at puberty when the complete test is used—though it still lags if the patch test only is under consideration.

These results agree broadly with those observed in other countries (Brailey, 1940) and with those of Schlesinger and Hart and of Bradshaw in London. There is little to be gained by detailed comparison, for which the reader is referred to Hart (1932).

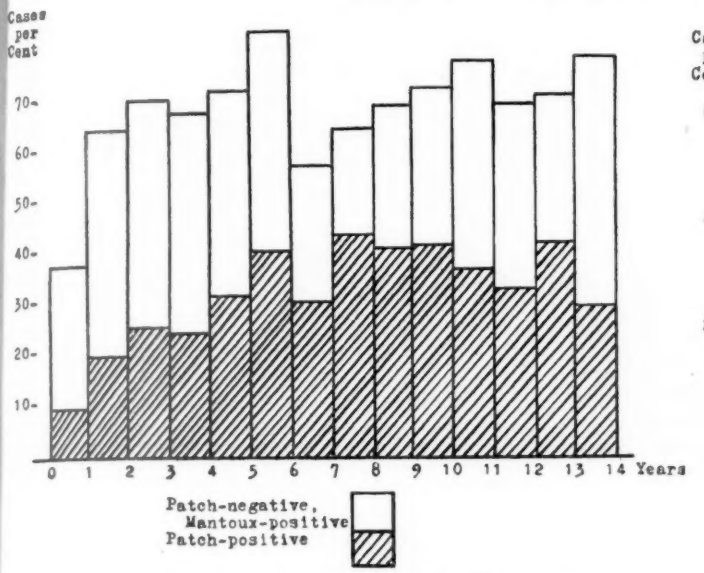

FIG. 1.—Tuberculin sensitivity in 1,050 contacts.

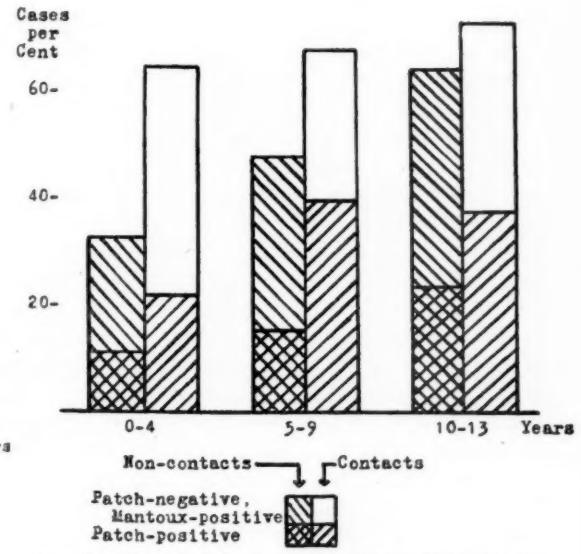

FIG. 2.—Tuberculin sensitivity in 1,050 contacts and 426 non-contacts.

who gives a complete review up to that date. The non-contact children in the present study are not a random population sample; they were all to some extent ill, and were mostly suspected of tuberculosis, though in fact only one in twenty actually proved to be suffering from that disease. That they showed much higher rates of reactivity than Jones Davies's series, for example, may be due to at least three factors: they were urban, as opposed to rural, dwellers; they were presumably ill, not presumably healthy; and they underwent a test more severe than the tuberculin jelly test used in the Welsh survey. The rates found by Heimann and Paterson in presumably healthy urban children (these workers also used tuberculin jelly) were also higher than those of Jones Davies, and correspond quite closely to our results in non-contacts with the patch test alone. This suggests that our sample was perhaps not greatly different from the population at large, especially as Court (1939) has found the patch test to be approximately equal in strength to 1 : 1,000 old tuberculin intradermally, which is also the equivalent strength claimed for tuberculin jelly (Jones Davies, 1943).

Those children who were x-rayed—that is to say, all who were tuberculin positive and all who did not undergo tuberculin test—showed the presence of calcified lesions within the thorax as enumerated in table 2. Calcification occurred as nodules in the lung field, or in the hilar lymph glands, or both. No special radiological technique was employed, such as over-penetration or radioscopy, so that a severe standard of interpretation was obligatory and the figures are, therefore, minimal.

TABLE 2
INCIDENCE OF CALCIFIED LESIONS

Age in years ..	0–4	5–9	10–13	Total
Contacts ..	9	34	40	83
Non-contacts ..	1	12	9	22
Total ..	10	46	49	105

Morbidity

Twenty-three of the 426 non-contacts, and 53 of the 1,050 contact children were found at the time

TABLE 3
CLASSIFICATION OF LESIONS

	Diagnosed at Clinic			Diagnosed elsewhere	Total
	Non-contacts	Contacts			
		1st exam.	Re-exam.		
Pulmonary tuberculosis (adult type)	2	2	—	—	4
Active primary	10	45	11	17	83
Pleural effusion ..	2	2	—	5	9
Cervical glands	6	2	1	9	18
Abdominal	—	—	—	3	3
Bones and joints ..	—	—	—	6	6
Phlyctenulosis	3	1	—	—	4
Miliary or generalized ..	—	1	1	1	3
Total	23	53	13	41	130

of first examination to have demonstrable tuberculous lesions. Re-examination of initially tuberculin-negative contact children, according to the technique described elsewhere (Thompson, 1944) detected conversion to positive reactivity in 52 cases, of which 13 were accompanied by evidence of gross tuberculosis. During the four-year period under review, in addition to the 89 cases of tuberculosis diagnosed at the clinic, 41 were referred for treatment or observation from outside sources, mainly hospitals, with the diagnosis already established.

The term 'active primary' includes cases of grossly enlarged intrathoracic lymph glands—with or without a distinguishable parenchymal focus—and 'epituberculosis,' or cases of lobar or lobular collapse, due to glandular pressure on a bronchus. Of the 66 cases diagnosed at the Clinic, 63 were patch-positive: the other 3 reacted negatively to the patch but positively to the intradermal test. The age distribution of these patients is shown in table 4. The incidence of tuberculous lesions was approximately equal when averaged for each year of age.

TABLE 4
AGE INCIDENCE OF TUBERCULOUS LESIONS

Years of age	Diagnosed at Clinic			Diagnosed elsewhere	Total
	Non-contacts	Contacts			
		1st exam.	Re-exam.		
–1	1	3	3	—	7
1–4	3	18	6	10	37
5–9	7	24	3	14	48
10–13	12	8	1	17	38
Total ..	23	53	13	41	130

Most of the children with lesions who were clinically ill were admitted to hospitals or sanatoria for treatment. Many of those who remained without symptoms were rested at home and observed as out-patients. With the few exceptions detailed in the following section, complete clinical recovery, with resolution of the lesions—often accompanied by progressive calcification—was the rule.

Mortality

Death occurred in seven of the children described above. None of the 426 non-contacts died. Of the 41 cases diagnosed outside the clinic as suffering from tuberculosis one case ended fatally—a child with generalized tuberculosis already moribund when notified. The six remaining deaths took place among the 1,050 contacts. All six children were in contact with a sputum-positive adult at or near the time of being found tuberculin-positive. The rapidity with which death ensued is in keeping with the observation of Wallgren that fatal generalization from a primary complex occurs almost invariably at about twelve weeks from the development of tuberculin sensitivity. The fact that follow-up of the whole group has not been prolonged, therefore, does not seriously affect the validity of our case-fatality rates. Prolonged illness with a fatal termination (Hurford, 1945) is sufficiently uncommon in childhood tuberculosis to be of relatively little statistical importance.

TABLE 5
FATAL CASES DIAGNOSED AT CLINIC

No.	Age in months	Sex	Tuberculin test	Evidence of tuberculosis	Survival (in weeks from being found tuberculin-positive)
1	7	M	Patch +ve	None. X-ray refused	8
2	7	F	Patch –ve; +ve. 15 mths. later	Acute miliary	2
3	9	M	Patch +ve	None. X-ray negative	15
4	12	F	Patch +ve	Acute miliary	5
5	13	F	Patch –ve; +ve. 3 mths. later	Meningitis	2
6	36	F	Patch +ve	Active primary complex	7

During the years 1942–45 there were eighteen deaths from tuberculosis (eight males and ten females) in children up to the age of fourteen in the boroughs of Acton and Ealing. Of these nine were known to the clinic before death. Seven have already been described; the other two were known before 1942, and were, therefore, outside the scope of our preliminary study. Of the remaining nine, one was in contact with a known case of tuberculosis, but routine examination had previously been refused. The mother of one was found to have sputum-positive tuberculosis. No source of infection was found in the other seven.

For all ages inclusive in the years 1942–45, deaths from all forms of tuberculosis in Acton and

TABLE 6
TOTAL DEATHS FROM TUBERCULOSIS IN CHILDREN, BOROUGHS OF ACTON AND EALING, 1942–45.

Age in years	–1	–2	–5	–10	–14	Total
Number of deaths	4	4	5	3	2	18

Ealing totalled 450, an average of 112·5 per annum. Deaths in children were 4·5 per annum, or 4 per cent. of the total. The adult population (about 170,200) had an annual death rate of 63·5 per 100,000, while the rate for children under fourteen (about 41,800) was 10·2.

Discussion

These figures should help us to examine tuberculosis in childhood both as a separate problem and in relation to tuberculosis as a whole. It seems that the population under review, even though the groups subjected to tuberculin test are not true samples, incurs a heavy rate of infection with the tubercle bacillus at an early age, and that this rate has a rapid annual increase. In spite of this, the deaths occurring during childhood from tuberculosis—which are by no means confined to the years of early infancy—are very few, both in absolute numbers and in comparison with deaths from other causes. Healed tuberculous lesions, with radiological evidence of calcification, are encountered at all ages. A large proportion of children show a low degree of sensitivity to tuberculin, being negative to the patch test but positive to a strong intradermal injection, which may be presumed to indicate a tuberculous infection becoming obsolete.

It would seem, therefore, that children in this district are able to resist tuberculous infection remarkably well. Even of those with massive intrathoracic lesions, only 1 in 83 failed to make an initial recovery, with or without institutional treatment. In this connexion, it is well to remember that there is nowhere in the literature any statistical evidence that sanatorium treatment and its ancillary methods have any influence on the fate of the primary complex, and Myers (1944) even advances positive evidence to this effect. One would not, however, deny the value of individual clinical observations (Roberts, 1943; Richards, 1944).

This does not mean that tuberculosis in childhood is negligible. Our material takes no account of residual illness from resolved primary lesions—such as bronchiectasis or peritoneal adhesions—or of the occasional case of late haematogenous dissemination. Nor can it help us to forecast the type of case that may develop pulmonary tuberculosis in adult life. The work of Israel and de Lien (1942) suggests that such a development depends less on the character of the primary infection than on the maintenance of contact with an infective source up to and during adolescence. In diagnosing large numbers of adults with pulmonary tuberculosis, it is remarkable how rarely one finds a history of tuberculosis in childhood. On the other hand, those adults actually in contact with infectious tuberculosis, and who themselves develop tuberculous lesions, do so, with very few exceptions (Thompson, 1944), either while still in contact or within eighteen months of the cessation of contact. Despite the allegiance of such authorities as Moncrieff (1945) to the continental view of endogenously-derived phthisis, we are constantly impressed by the important part played by immediate external infection in adult life. We do not, however, allow this to divert us from the task of breaking contact between children and an infectious source, preferably by isolation or by treatment of the infected patient, otherwise by boarding out the children under the usual Local Authority arrangements. We are extremely reluctant to segregate young children in institutions, as is sometimes advocated (Carling, 1946). Such a policy would be uneconomical in view of the large numbers and the necessarily prolonged periods of stay involved. Moreover, it is fundamentally undesirable for social and psychological reasons. The experience at Lymanhurst (Myers, 1944) suggests that the ' preventorium ' system has no discernible effect on mortality from primary tuberculous infection. Our figures indicate that this mortality is in any case small, and that the fatal cases are so fulminating that any known treatment is useless.

It seems probable that children who are sick are usually, though not always, better off in hospital. Children with sub-clinical lesions may be hospitalized if home conditions are poor, but a good home and a good mother may be preferable if no special treatment is indicated, especially if the child is under school age. In children who are tuberculin-negative, infection must be prevented at all cost, or forestalled by B.C.G. inoculation or its equivalent, though the latter is in our opinion a poor compromise, abounding with administrative difficulties. When a child is already infected, tuberculin-positive, but clinically not ill and without a demonstrable lesion, it is the practice to break contact with the infectious source just as if infection had not already occurred. This is on the assumption that repeated infection carries an increased danger, an assumption that is constantly reiterated in textbooks (Miller and Wallgren, 1939), although it has never been proved, and is contrary to most experimental work. The child's reaction to a primary tuberculous infection is in several respects different from the adult's, and children may thus react differently to repeated, as opposed to a single, exposure. More factual information is required before the thesis can be accepted that re-infection is an additional

menace to children; the assumption of the thesis as a practical safeguard is meanwhile justifiable.

Conclusions

In the absence of large-scale tuberculin testing of true population samples, selected groups studied at the Ealing Chest Clinic give some guide to the incidence of tuberculous infection at different ages in childhood for the population concerned. The patch test has proved a reliable index of a relatively high degree of sensitivity to tuberculin. Results of epidemiological value, however, require the use of intradermal tests equal to at least 1/100 old tuberculin in children negative to the patch test. The patch test alone will detect sensitivity in most cases of active tuberculosis with manifest lesions. Routine examination of children known to have been in contact with tuberculosis will reveal active tuberculosis in a proportion at least as high as that found in children who are not known contacts but who have symptoms. The highest incidence of manifest lesions is found in children at the time of conversion from a negative to a positive tuberculin reaction. Negative reactors should, therefore, be repeatedly re-tested so long as the risk of infection continues.

The immediate prognosis of tuberculous primary infection in childhood, with or without a demonstrable lesion, is, from the statistical point of view, good. The mortality rate among patients attending the clinic was exceedingly small. Those children who died, did so within three or four months; in general there was no early indication that might aid prognosis. Of the total deaths from tuberculosis in children, the majority occurred suddenly, in the absence of a history of contact or of prolonged illness. It, therefore, does not appear that medical treatment can be expected to influence the outcome in children with primary tuberculous infection, or that the detection of a higher proportion of such cases by intensified diagnosis is likely to diminish the general mortality. We cannot say whether any given child will or will not undergo a rapid and fatal generalization of the disease, nor probably have we at present power to influence the issue. We can predict with some confidence a more or less complete recovery if the first three months are survived. Beyond that we can only speculate. The proportion of surviving children who will later develop haematogenous lesions in bone or kidney is probably very small indeed. Those who will develop phthisis after adolescence are more likely to do so by reason of continued or resumed contact with an outside source of tuberculous infection during that later period, than because of the character of their primary infection. The cleaning out of infectious tuberculosis from each household, therefore, becomes a paramount object.

For these reasons it would seem that the mortality from tuberculosis in childhood can be substantially reduced only by discovering and eliminating infectious tuberculosis in adults, and our energies should be concentrated to this end.

Summary

A study is presented of all children examined at the Ealing Chest Clinic during four successive years, in relation to the total mortality from tuberculosis in children in the district during the same period.

The incidence of sensitivity to patch and intradermal tuberculin tests, of calcified lesions, and of active manifest tuberculosis, is compared in children who were, and children who were not, known to have been in contact with tuberculosis.

A policy is sought for rationalizing the control of primary tuberculous infection and disease in children.

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PURPURA NECROTICA

A POSSIBLE CLINICAL APPLICATION OF THE SHWARTZMAN PHENOMENON*

BY

J. H. SHELDON, M.D., F.R.C.P.

(From the Royal Hospital, Wolverhampton, and the Hallam Hospital, West Bromwich)

This paper describes a disease entity which does not appear to have been previously recorded in Great Britain. It is based on three cases all affecting female children, two of which occurred in 1943, and the third in 1945. These children came from different towns in Staffordshire and had no connexion of any kind with each other.

Case Reports

Case 1. A female, aged five years, was brought to the out-patient department at the Royal Hospital, Wolverhampton, on February 24, 1943, on account of purpura, and was admitted at once.

There was no previous history of illness. The present illness began suddenly on February 17, 1943, with pains in the legs (which lasted for one week). Two days later there was swelling of both ankles which lasted for twenty-four hours and then disappeared, leaving a bruise. The next day bruising was noticed on the inside of the knees and on the buttocks, but the child went to school. When she happened to fall down the bruises were noticed and she was sent home, where she remained till she came to hospital four days later on account of a purpuric rash which had appeared in the meantime.

On admission both legs and buttocks were covered with purpuric patches of a peculiar character, the remainder of the body being free apart from a few small isolated lesions, and the mucous membranes were not affected. When discrete these purpuric patches all had the same appearance. They were of all shapes; some were circular or oval, but there was a definite tendency to angularity, the appearances being precisely similar to those of the next case (see fig. 2). They were raised above the surrounding skin, with a definite edge, and had a black, haemorrhagic bulla at their centre. Their general appearance is best described as a haemorrhagic urticaria. In addition to the discrete lesions there were a few areas of confluence where one simply saw a large purplish-black area. The two largest were on the outside of the left buttock and thigh, and these lesions attracted immediate attention on account of their remarkable shape. That on the thigh was shaped like a rectangle sharpened at one end, having a flat top and sides which converged downwards almost to a sharp point below, the whole appearance being distinctly artificial. The one on the left buttock had an even more artificial shape, being distinctly triangular except that one side was somewhat curved. Both areas were surrounded by a thin red inflammatory margin. All the four small toes on each side were black from their junction with the foot. The child's general condition was better than one would expect from the severity of the local lesions, and the temperature was only slightly raised (99° F.). Both knees and ankles were somewhat swollen and tender, but there was no limitation of movement. Blood count was normal (see below). Routine physical examination was entirely negative.

The disease had reached its maximum by the time of admission and no new lesions appeared thereafter. The subsequent changes in the purpuric areas were unexpected, for instead of gradually fading to a brownish colour and disappearing, an entirely different course of events occurred. In the first place the lesions during the next two or three days became very hard. The black skin covering the small toes was so stiff that the child could not move the toes; while the confluent areas on the left thigh and buttock became so hard that tapping them with the finger-nail gave the same impression that would be given by tapping a plaster-of-Paris bandage. This hardness of the lesions was a very striking clinical feature, and suggests that there had been a coagulation of the tissues involved.

The next and final stage was that of separation. The smaller discrete lesions peeled off as a scale of black epithelium, leaving pink and healthy new skin below. The black skin over the toes split and peeled off in a similar way, and the same sequence occurred in the confluent areas except for the two large ones on the left thigh and buttock. These began to separate at their edges, and it was at once apparent that deep necrosis had occurred. The slough from the oblong lesions on the thigh came away in about ten days, leaving a deep trench which had removed the whole depth of the subcutaneous tissues down to the fascia. The triangular patch on the left buttock went much deeper; the slough, which

* Based on a communication to the Association of Physicians of Great Britain and Ireland on April 12, 1946.

took fourteen days to separate, left a deep dome-shaped cavity extending approximately half way into the substance of the gluteal muscles. These cavities were lined with clean granulation tissue, and the moment the sloughs had separated the child's general condition became quite normal. The wounds then granulated uneventfully and became covered with skin, though owing to their size this process took three months, and although the activity of the disease had ceased at the end of February, the child was not discharged from hospital until the end of May, 1943. There were no symptoms after this date, but owing to the size and depth of the lesions there was extensive and permanent scarring of the left buttock and thigh, which is shown in fig. 1, p. 17. They cause no disability.

Case 2. A girl, aged three years, was admitted to the Hallam Hospital, West Bromwich, on March 20, 1943. At eighteen months she had been immunized against diphtheria. In 1942 she had a generalized 'dermatitis' and also impetigo. She had then been well until February, 1943, when she had measles complicated by a right otitis media, from which she made a good recovery. She had been up and about for a fortnight before the present illness appeared. This began suddenly on the morning of March 17, 1943, when the mother noticed haemorrhagic areas on the back of the right lower leg, and the child was obviously not feeling well. On the evening of the same day a further haemorrhage appeared in front of the right ankle. Nothing further happened for thirty-six hours, when (March 19) a large haemorrhagic area appeared on the left buttock, and next day she was admitted to hospital.

On admission she was obviously a very ill child, pale and fretful, and in addition to the haemorrhagic areas already mentioned there were numerous smaller purpuric patches which, as in the previous case, affected almost exclusively the buttocks and legs. They were precisely similar to the individual lesions of case 1, being either rounded or having the same straight-sided geometrical or triangular outlines, were raised above the surrounding skin, and had the same central black haemorrhagic bulla. An isolated lesion on the shoulder is illustrated in fig. 2, p. 17. The temperature was normal, and routine physical examination revealed no abnormalities. The disease was still active, for the next day the right buttock became involved, a number of violet-coloured areas appearing and rapidly increasing in size to coalesce into one large area. This involved the whole right buttock and part of the adjacent thigh and contained a small islet of healthy skin which remained unaffected. This lesion had a distinctly artificial appearance, being more or less square-shaped, and its upper margin was formed by a particularly straight horizontal line. That on the left buttock was rather smaller and more rounded. On both sides there were prolongations passing inwards towards the perineum under the ischial tuberosities. As in the previous case, these large confluent areas were surrounded by a thin red inflammatory border. A week later, on March 28, 1943, the eyelids on both sides, the dorsum of the left hand, and the left heel became oedematous, and by March 30 both hands and the dorsal surfaces of both feet were also involved. On the same day the fronts of both knees became covered with haemorrhagic patches. These were thought to have resulted from pressure, for owing to the state of the buttocks the child could only lie on its face, and when awake it liked to rest in the knee-elbow position. The period of active illness now ceased, no further lesions appeared, and the child's general condition began rapidly to improve. The process of recovery went through the same stages as in case 1. There was the same preliminary hardening of the lesions, to an almost stony hardness, which then healed by desquamation of a patch of hard black epithelium, leaving healthy new skin beneath, while the larger areas which extended down into the deeper tissues healed by the separation of a large slough. This phase gave rise to great anxiety, for it soon became obvious that the sloughs in the buttocks went very deep indeed, and the risk of haemorrhage appeared sufficient to call for the constant presence of a special nurse provided with a bell and a tray of appropriate instruments. (The nursing difficulties were increased by the necrosis simultaneously present on the front of both knees, and the child's recovery under these circumstances is a tribute to the care of the nursing staff.) Separation was, however, quite uneventful, though it took twenty-one days to accomplish. This stage of the illness is shown in fig. 3 from which the great size of the necrotic areas can be realized. When the sloughs had come away, large clean cavities were exposed, covered with healthy granulation tissue, which from their size suggested large gunshot wounds. That on the right buttock was of enormous size and went very deep into the substance of the gluteal muscles, reaching almost to the bone. It is probable that the outer aspect of this buttock was only saved from complete destruction by the islet of unaffected skin; this was supported on a cone of tissue rising from the depths of the wound, and it thereby reduced the volume of tissue destroyed. The wounds gradually granulated and became covered with new skin as in case 1, except that owing to the larger size and greater depth of the lesion, skin-grafting had to be undertaken on the right buttock. Difficulties were experienced in this owing to the amount of fibrous tissue in the scar, with a resulting poverty of blood supply, and it has taken two years for the area to become completely healed. Ultimately six permanent scars have been left, one on each buttock and one at the back of the right ankle, which are illustrated in figs. 4 and 5. The scar on the right buttock covers an area of approximately eighteen square inches (see fig. 5). On the front of the legs there is a wide but superficial scar over each patella, and above the inner

aspect of the left knee is a small rounded scar resulting from a deeply penetrating necrosis which reached almost to the femur. The child has been quite healthy since her illness.

These two girls obviously suffered from the same disease. The next case is thought also to be an instance of the same condition, though it was much less severe.

Case 3. A girl, aged eleven months, had been breast-fed for three months, and the previous history was uneventful. On March 5, 1945, she had a nasal discharge resembling that of, and probably due to, coryza, and which her doctor diagnosed as due to a cold in the head and teething. On the afternoon of April 16 the child became very miserable and moaned a good deal, so that the mother thought she had been too much in the sun, it being a very hot day. On April 17 a transitory rash appeared, which the mother says consisted of ' red, mottled marks,' affecting the face, back, arms, and legs. The mother thought this might be measles, but the doctor thought it was a heat rash; the spots appear to have been raised. When the napkin was changed on the morning of April 17 the buttocks were normal, but when they were later changed at midday the mother noticed a black bruise high on the inside of the right buttock. At the same time the child became even more fretful, she cried whenever she was touched, and, according to the mother, ' every limb seemed to ache.' On the next day (April 18) she lay still in bed, which was very unusual, and on April 19 the fingers and dorsum of both hands were swollen, and she was admitted to the Royal Hospital, Wolverhampton. Deep in the upper part of the fold of the right buttock was a small purplish-red area approximately half an inch in diameter, and there were red, tender swellings on the right palm and at the base of the right ring finger. There was no rise of temperature; the child was very fretful, had some photophobia and marked general muscular hypotonia. No further incidents developed, and in the course of the next week the area on the right buttock became black and hard as in the two previous cases, and during this period subcutaneous haematomas formed in the swellings on the hand. Whereas, however, the lesions on the hand disappeared by absorption, that on the buttock separated as a slough, leaving a surprisingly deep wound reaching to the muscle, and lined, as before, with clean granulation tissue. The slough took twelve days to separate, and after this there was an immediate improvement in the child's general condition, which rapidly became normal. The wound healed satisfactorily, leaving a scar with a number of lateral prolongations, and is shown in fig. 6, p. 17. Since then the child has been healthy.

In none of these three cases did routine physical examination reveal any abnormalities, the mucous membranes were unaffected, there was no enlargement of the spleen or lymphatic glands, and, apart from a rise of temperature to about 99·4° F. at its height, the disease was afebrile.

Laboratory investigations. These were necessarily limited, owing to prevailing war conditions.

URINE. Urine was normal in cases 1 and 3; in case 2 it contained a slight haze of albumin at the height of the illness.

BULLAE. Cultures of the haemorrhagic bullae were sterile.

BLOOD COUNTS. The blood counts and differential counts are shown in the table.

In case 2 the bleeding time (March 22) was $2\frac{3}{4}$ minutes, and the clotting time $5\frac{1}{2}$ minutes.

Changes in the blood picture were secondary in nature, there being merely an anaemia at the time of the haemorrhage and a leucocytosis during the phase of sloughing.

Summary of Clinical Symptoms

These three cases clearly suffered from the same disease, though the illness of the baby was much the least severe. The disease appears to begin without warning, for there is nothing common to the preceding history of the children; one had had no previous illnesses at all, one was convalescent from measles and had had an attack of impetigo a year previously, while the baby's only illness was a coryza a fortnight before. The acute phase lasted from approximately four to fourteen days, and was characterized by a group of symptoms typical of anaphylactoid purpura. Between them these children exhibited varying combinations of pains in the limbs (all cases); swelling in knees and ankles, followed by bruising (case 1); subcutaneous swellings affecting the eyelids, hands, and feet (cases 2 and 3)—followed once by a subcutaneous haematoma (case 3); and transitory red mottled rash (case 3). The two elder children had a very severe purpuric rash, which was limited to the buttocks and legs apart from a very few scattered lesions over the shoulders. The detailed appearance of the purpuric patches was characteristic of anaphylactoid purpura; they were raised above the surrounding skin, with a distinct edge, and showed a thin red margin at their periphery, while the centre of each had a black haemorrhagic bulla. Their only remarkable feature was a tendency to an unusual angularity of shape. All three cases had one or more areas of confluent purpura, which were remarkable for the geometrical shape of the larger areas, especially the triangular patch in case 1 and the rather square-shaped area in case 2. This acute phase of the illness was virtually afebrile, had no visceral manifestations, no affection of the mucous membranes, and no significant changes

	Date	Hb %	Red Cells	Colour index	White cells	Blood platelets	Differential Counts				
							Polymorphs %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
Case 1	25.2.43	69	3,540,000	0·97	10,600	'Not diminished'	57	36	6	1	—
Case 2	20.3.43	60	3,000,000	1·0	20,000		59	28	10	1	1
	30.3.43	58	2,900,000	1·0	22,000	190,000 per c.mm.					
	13.4.43	62	3,200,000	0·96	17,900						
	3.5.43	70	3,500,000	1·0	12,100						
Case 3	22.4.45	63	5,980,000		21,200		28	57	6	4	5
	1.5.45	65	5,320,000		11,600						

in the blood picture. The precise order of appearance of the clinical features varied somewhat from case to case; cases 1 and 3 began with pains in the limbs and general constitutional disturbance, while in case 2 areas of haemorrhage were the first manifestation.

After the acute phase recovery began at once, and took the same course in all cases. The initial stage was one of hardening of the lesions, which was a striking clinical feature and presumably indicated a coagulation of both the effused blood and the tissues concerned. After this the discrete purpuric lesions peeled off as a flake of hard black skin, leaving healthy new skin below. The larger areas of confluent purpura separated as sloughs, taking from ten to twenty-one days in the process, and leaving healthy cavities—lined with healthy granulation tissue—which in the more severe sites had extended deep into the underlying muscle. The moment the sloughs had come away the children were back in good health, and all that remained was for the cavities to become filled up with granulation tissue and covered with new skin. This process took six weeks in the case of the baby, three months in case 1, and two years in case 2. Case 2 has the largest scar, a patch on the right buttock covering some eighteen square inches. The children have been quite healthy since. The general picture was, therefore, one of an acute and short illness followed by a prolonged period of repair; except for large and permanent scars there was no permanent disability.

Cases from the Literature

There appear to be only two cases of a similar nature reported in the literature. The condition was first described by Martin de Gimard in 1884, and a further case was reported by Beinhauer in 1929.

Martin de Gimard's case. The original account has not been available, and the following précis is taken from a transcription by P. Chevallier (1937).

A child, aged eight years (de Gimard's case 10), suddenly developed oedema over the malleoli; six days later there was a swelling on the face and left shoulder, and as the oedema disappeared the right side of the face became violet. By the eighth day the right side of the face and neck was occupied by an enormous 'wine-coloured' swelling, which in places was violet and contained islets of healthy skin. There were similar large swellings on both arms. On the eleventh day violet patches appeared on the ear, and on the twelfth day there was swelling of the right thigh. By the thirteenth day gangrene had appeared on the cheek and upper lip, and the upper parts of the arms were covered with black scabs. The area of gangrene on the upper lip separated on the eighteenth day, and that of the cheek on the twentieth day; in the succeeding days further areas of necrosis separated from the chin, the upper eyelid and the left forearm, removing the muscles and extensor tendons and exposing the olecranon. The child made a complete recovery, but was left with permanent and extensive scarring of the face and arm.

Beinhauer's case. Under the title 'Purpura haemorrhagica gangrenosa,' Beinhauer (1929) reports the case of a male aged twenty-eight months.

The illness began with pain in the left ear. Two days later the child had pain in the left ankle, with a diffuse bluish-red discolouration of the whole foot, and during the next two days he developed haemorrhagic areas on both thighs, the left elbow, and the right hand. On admission to hospital the entire left foot, from the toes to four centimetres above the ankle, was covered by a purplish-red haematoma which was stony-hard, and above it there were smaller haematomas. The whole antero-lateral aspect of the left thigh and the postero-lateral aspect of the right thigh were covered with similar stony-hard purplish haematomas. There was a similar lesion on the left elbow and the right hand and fingers; this had a fusiform appearance owing to haemorrhage into the joints. Both buttocks were involved in a haematomatous infiltration which was continuous with the lesions on the thighs and penetrated inwards to the perineum. All these lesions had bullae filled with effused blood. During the next few days the lesions became gangrenous and began

to separate, removing the muscles and exposing the underlying bone. (A photograph taken at this stage shows exactly the same process as that depicted in fig. 2.) In view of an absence of thrombocytes from the blood splenectomy was then undertaken, together with amputation of the left foot and two fingers, but septicaemia developed and the child died three weeks after the operation.

Beinhauer lays stress on the following features, all of which are duplicated in the cases reported in this paper: (1) the stony-hard consistency of the necrotic areas, (2) their sharp definition from the surrounding healthy skin, and (3) the absence of any signs of absorption, the haemorrhage progressing directly into necrosis. The condition appears to have been afebrile until the septicaemia supervened.

There can be no doubt that both these cases are examples of the same condition as that reported in this paper. The term ' purpura haemorrhagica gangrenosa ' which was used by Beinhauer has also been applied to cases in which a purpuric process followed by local gangrene has formed part of a septicaemic process. Martin de Gimard's case 8 was of this type, and a further instance was reported by Chevallier (1937). Michael's case (1920) was also probably of this type. A child, aged two years and a half, had intermittent attacks of purpura over some five months, associated with a temperature rising to 104° F. The child developed gangrene of the terminal phalanges of seven fingers and also of the left thigh and right buttock, ending with loss of the terminal phalanges. The child made an otherwise complete recovery. In a recent article, Marie and others (1946) have described four children who developed gangrenous purpura in the course of a meningococcal infection. The lesions resemble those under consideration in that they were indurated and had a sharp border, as if ' traced with a pen,' and a raised edge; but the necrosis was only subcutaneous, and scarring was not a prominent feature. The nature of these purpuric lesions associated with a septicaemia raises questions of great interest, but the differences appear sufficient to justify their clinical separation from the purpura of unknown origin followed by necrosis extending deep into the muscles which is the subject of this paper. In all five cases there has been no temperature and no evidence of infection; the bullae from the lesions in case 2 were sterile.

Discussion

In attempting to elucidate this condition, it is clear that it begins with an illness which is indistinguishable clinically from allergic purpura, though why all such purpuras do not follow the same course remains a puzzle. It appears also to be a disease of children, the recorded ages being eleven months, twenty-eight months, two and a half, three, five and eight years. It is also clear that the peculiar geometrical shape of some of the larger lesions is a feature which demands clinical explanation, for they are clearly artificial. It is impossible to imagine a general pathological process which, free from all restraint, would exteriorize itself in angular areas independent of all anatomical considerations. The scars shown in figs. 1 and 5 have distinctly artificial appearance, especially the straight sides joined by a right angle at the left upper corner in fig. 5. It would appear certain that they must be artificial in the sense of being self-inflicted though not, of course, deliberately so. There are two indications from the clinical histories which agree in suggesting that relative stasis may be an important factor. These are: (1) the localization of the generalized purpuric rash to the buttocks and legs; and (2) the appearance of areas of confluent haemorrhage on the front of the knees in case 2. There were three such areas, one over each patella, and a deep one just above the inside of the left thigh just above the knee. These did not appear till the eleventh day of the illness, and they coincided with angioneurotic oedema of the eyelids and hands. Their appearance at these sites was undoubtedly due to the fact that owing to the large lesions on the buttocks the child had to be nursed on its face and always liked to get into the knee-elbow position.

There is one possible approach to the geometrical outline of the larger lesions which will at the same time explain their localization. In case 1 we have to explain a triangular scar on the left buttock, and a tapering scar on the left thigh (see fig. 1). It is common to see linear marks on the buttocks of patients caused by pressure from the crumplings and folds of their pyjamas, and such lines at times mark out a triangle. At other times one sees areas of redness on the buttocks due to differential pressure from crumpled and non-crumpled areas of pyjama, and these areas are often geometrical in outline. Is it possible that the triangle on the buttock of this case was marked out in this way while the child was lying asleep on its left side? If so, the tapering scar lower down on the outside of the left thigh receives a similar and ready explanation. Such an explanation involves, however, the further assumption that during the active period of the disease there is a critical phase (or phases) of very short duration within which the sensitizing process reaches a sharp maximum, so that quite slight but continued pressure during this short period can, with the accuracy of a carpenter's pencil, mark out areas on

the skin subsequently to be the site of deep necrosis. Such an assumption provides a ready explanation of the general localization of the scars in case 2 (see fig. 4). There are large areas on each buttock—each of which has a process passing inwards under the ischial tuberosities—and a scar at the back of the right lower calf. The general appearance at once suggests that the child was sitting in a chair at the time the lesions were marked out. The chair habitually used was an ordinary high nursery chair for feeding the child at table, and the parents were in the habit of putting a large square pillow on the seat. Measurements show that this would have risen round the buttocks of the sitting child to approximately the height of the straight line marking the top of the scar on the right buttock, while the square-shaped outline of the upper portion of this scar is just such as could have been caused by pressure and creasing from a pillow. It is also easy to imagine how such pressure could leave an area of skin unaffected, like that present in the scar on the right buttock. The parents further state that the child used to like to loll on one side with one foot on the foot-rest and the other hanging down and resting against the upright of the chair. Such a position would account for the greater depth of the lesion on the right buttock, and for the presence of a scar at the back of the right ankle and the absence of one from the left foot. A similar explanation is also applicable to the small scar high up in the fold of the right buttock in the case of the baby. The child was very fretful during the first two days of the illness, and the lesion in this situation may well have derived from pressure of the mother's hand or fingers while nursing it. The localization of the lesions in Beinhauer's case is difficult to explain, but the necrosis of the right side of the face in Martin de Gimard's case could easily have been delineated by pressure from the pillow while asleep.

It is, therefore, a reasonable clinical deduction that both the localization and the peculiar shape of the larger lesions in all three cases could have been due to slight but continued pressure acting during a critical phase—lying asleep on the left side in one case, sitting in a feeding-chair in another, and being nursed in the third. The lesions on the front of the knee in case 2 appear to be in a somewhat different category; they arose as the result of pressure continued over several days towards the close of the active period of the illness, when the child liked to be in the knee-elbow position owing to the state of its buttocks. Those on the knee-caps left quite superficial scars, while slightly above on the inside of the left knee was a small but deep area of necrosis. If the explanation advanced above for the larger areas is the true one, it has to be supposed that in the later stage of the disease any critical periods were of less intensity, and that is why long-continued pressure did not produce lesions of the same severity.

The only pathological process which will in any way meet these clinical requirements appears to be the Shwartzman phenomenon (1937). In this, a haemorrhagic necrosis is produced by two consecutive injections of a bacterial filtrate from a suitable organism. The first is given intradermally and the second intravenously some twenty-four hours later. There then develops at the site of the original intradermal injection a lesion which Shwartzman describes as follows: 'Four hours after the intravenous injection there appeared severe haemorrhagic necrosis at the prepared skin site. In the gross it was dark blue, swollen, with an angry red periphery, and histologically it showed disruption of the venules, extensive haemorrhage, thrombosis, and necrobiosis of all the cells. The reaction extended from the superficial layers of the skin through the entire thickness of the abdominal wall to the peritoneum' (p. 29). 'In typical strong reactions the early appearance is that of a crop of petechiae which continuously increase in size until there results an extensive confluent haemorrhage forming a sac filled with blood. The colour rapidly changes from blue to violet and almost black. There is an angry red zone at the periphery. The entire process may be so rapid that the petechial stage is indistinguishable' (p. 12). 'The healing of the strongly haemorrhagic lesion is slow. Sloughs which may form in about forty-eight hours after the intravenous injection are followed by gradual separation and scarring. The complete process of healing takes about ten days.'

The description of these experimental lesions coincides closely with the clinical appearances found in the three cases described. The initial development of purpuric patches in the skin which rapidly become confluent, followed by a deep necrosis involving the underlying muscles leading to the separation of a deep slough with subsequent scarring, presents a sequence of events of striking similarity in both the experimental and clinical phenomena. No histological examinations were made in the three cases under description, but fortunately Beinhauer examined the necrosis in the amputated foot of his case. This was characterized by inflammatory changes, mainly seen as a perivascular infiltration of white cells, together with widespread vascular dilatation and thrombosis; the deeper veins of the corium were completely occluded by thrombosis. These changes are closely similar to those described by Shwartzman. Shwartzman

considers that an essential feature of his phenomenon is the escape of active material in the preparatory injection from the circulation into the tissue spaces, so rendering the tissue cells sensitive. The state of the blood vessels in the skin and subcutaneous tissues during the early phase of the disease—marked by such phenomena as angioneurotic oedema and swelling of the joints—would provide a ready mechanism for this. Shwartzman found that a definite time interval was required between the two injections, the skin not becoming reactive until eight hours after the first injection and becoming inactive again after thirty-two hours. The optimum period was twenty-four hours, and it seemed a possible inference that such an optimum period corresponded with the demarcation of the sites of maximum necrosis in the cases recorded. In further experiments, however, Shwartzman found that it was possible to replace the initial intradermal injection by an intravenous one, provided there was local stasis and hyperaemia. In the relevant experiments (p. 197), intravenous injections were made into the vein of a rabbit's ear clamped at the base and exposed to heat to induce hyperaemia. Such ears invariably gave a marked reaction to the second provocative injection, and the appropriate state could be reached in a period of time from one-half to two hours (p. 336). Such a time-interval is of the appropriate length for the clinical requirements, which suggest that the larger areas of necrosis may have been delineated by local stasis from lying in bed on one side or sitting in a feeding-chair.

In view of the close agreement between the clinical and experimental data, it is suggested as a working hypothesis that these cases may represent naturally occurring instances of the Shwartzman phenomenon, for which the title of ' purpura necrotica ' appears to be suitable.

Summary

Three cases are described of an illness which appears mainly, if not exclusively, to affect children. It begins with features typical of an attack of allergic purpura; the purpuric lesions are associated with necrosis of the tissues affected, and healing is accompanied by separation of the resulting sloughs. These vary in severity from necrosis of the superficial layers of the skin to lesions penetrating deep into the underlying muscles, resulting in severe and permanent scarring. It is suggested that the disease may be connected with the Shwartzman phenomenon, and that in the early stages it may be characterized by short, critical phases during which the operation of slight but continued pressure may determine areas subsequently to be the site of deep necrosis. The illness leaves no sequelae apart from the scarring.

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(*For Illustrations of this Article see page 17*)

CHRONIC INTUSSUSCEPTION IN INFANCY AND CHILDHOOD

BY

W. G. WYLLIE, M.D., F.R.C.P.

Physician, Hospital for Sick Children, Great Ormond Street, London

and

R. J. PUGH, M.B., M.R.C.P.

Late Registrar, Hospital for Sick Children, Great Ormond Street, London

It is often stated that chronic intussusception occurs mostly in older children, at about the seventh year. Three cases of this sort in boys aged seven, seven and a half, and eight years, have recently been recorded by Garvie and Kemp (1945), who appended a list of sixty-two previous case reports of chronic intussusception in which the ages of as many as thirty-three were in the first three years of life. In their case, aged seven and a half years, the history suggested that the onset of intussusception was at two and a half years of age. The term chronic is used to imply many days, weeks, or even years, without or until the occurrence of acute obstruction. An intermittent form can also be recognized.

A further three cases of chronic intussusception with unusual features in infants under three years of age are here described, and a fourth case, which appeared to undergo spontaneous reduction on two occasions, is also recorded.

Case 1. A male infant came under observation at the age of three months (November, 1944) and was subsequently admitted to hospital for investigation on four occasions.

HISTORY. The infant weighed 7 lb. 2 oz. at birth, but made slow progress in spite of breast feeding, weighing 8 lb. 3 oz. at three months. He was then brought to hospital because of loose stools with blood for three days and vomiting feeds for twenty-four hours. The abdomen was soft, not distended, and dehydration was not present. Vomiting gradually ceased in hospital and the stools became more satisfactory, though occasionally streaked with blood.

A possible intussusception was thought of, but rectally nothing was found; a barium enema was attempted with an indefinite result, and a barium meal appeared normal on follow-through by x rays.

A mild degree of otitis media was present. The white blood cells were 10,500 per c.mm., of which 26 per cent. were polymorphs and 66 per cent. lymphocytes; Mantoux test and Wassermann reaction were negative. A month after admission the infant developed signs of pneumonia with rapid respirations and raised temperature, but made a good recovery on sulphadiazine. The infant took an adequate feed reluctantly and weighed only 8 lb. 12 oz. on discharge, aged five months.

The second admission was one month later for refusal of feeds and reappearance of abdominal pains. The stools were about three a day, yellow, and containing mucus. The weight was 9 lb. 3 oz. The abdomen looked distended, and, on palpation during a feed, a mass at the epigastric level was felt, which was of uniform consistency during palpation and was interpreted as a moderate hepatosplenomegaly. Under anaesthesia, the shape and consistency of the abdominal mass seemed to confirm the opinion of hepatic and splenic enlargement. Various diagnoses were considered, but not confirmed, including von Gierke's disease in view of one initial very flat adrenaline-sugar curve. The infant gradually gained weight up to 10 lb. 5 oz. at eight months.

Under out-patient observation, from the age of eight to ten months, it was found that a steady but poor gain in weight occurred up to 12 lb., and bouts of abdominal pain were reported, but there was no irregularity of the stools except a tendency for these to be loose and offensive. The abdominal mass was felt on all occasions and thought to be increasing in size. Again, on the third admission to hospital, an x ray and barium meal appeared to be normal.

The final admission was at eleven months, because of spasms of abdominal pain, frequent stools with occasional blood staining, and a temperature of 101·2° F. The white blood cells then numbered 17,000 per c.mm. The weight was 11 lb. 11 oz. On this occasion a barium meal outlined an obvious intussusception along the descending colon, but the infant collapsed and died before operation could be undertaken.

Post-mortem examination revealed a large intussusception involving the lower part of the ileum, caecum, and ascending and transverse colons invaginated into the descending colon. The duration of symptoms was eight months, with gradual increase in size of the abdominal mass, which at all examinations was never felt to contract or alter its shape.

Case 2. A girl, aged two years six months, was

admitted to hospital with a history of vomiting for ten days, with abdominal pain, marked anorexia, and constipation. There had been no blood in the stools. The previous health of the patient had been satisfactory.

EXAMINATION revealed a flushed, irritable child, rather poorly nourished, whose temperature was 99·8° F. and weight 26 lb.; the abdomen was tense and distended, making accurate palpation difficult and apparently painful. Rectal examination revealed no abnormality, and the other systems appeared normal.

A Mantoux test 1/1,000 was negative, the blood sedimentation rate raised to 18 mm. in one hour, and x ray of the chest and abdomen reported normal.

The abdominal pain continued intermittently, and guarding was noted in the epigastrium. Three days after admission, a blood-stained constipated stool was passed and it was thought that something could be felt on rectal examination. A laparotomy was performed by Mr. Twistington Higgins, which revealed an intussusception with an apex of distal ileum down to the pelvi-rectal junction. Manual reduction was effected except for an irreducible three inches of ileo-ileal intussusception which required resection. The proximal gut was exteriorized with a Paul's tube, and the distal portion by tying in a de Pezza catheter.

The immediate postoperative period was precarious, but was survived by means of intravenous fluids and duodenal suction. A second operation, consisting of a side-to-side anastomosis of the terminal ileum, was performed one week later. The patient's general condition necessitated liberal intravenous infusions of reconstituted plasma, blood, and glucose saline, for the succeeding ten days. Eventual recovery was complete five weeks after the first laparotomy and subsequent progress has been uneventful. Duration of intussusception was about thirteen days.

Case 3. A girl aged two years two months was admitted, in August, 1945, for investigation of a long and vague history of ill health. The patient was an only child, born weighing 5 lb. 7 oz.; she thrived well on breast feeding until ten months, when for a period of one month she passed a great deal of unchanged blood in her stools, had frequent vomits, refused feeds, and lost weight rapidly.

A rectal swab at the onset of the diarrhoea provided a growth of Sonne dysentery B., and the patient was isolated at a fever hospital. After four weeks, improvement had taken place, but the diarrhoea and vomiting recurred ten days after her return home, still with streaks of blood in the stools. No further intestinal pathogens were discovered.

On first attendance at the Hospital for Sick Children, at the age of fifteen months, a history was given of bouts of abdominal pain, usually of daily occurrence but absent for two periods of four weeks each. The pains were associated with frequent, loose, pale stools without blood staining. At this time the patient weighed only 15 lb. 10 oz., and was pale and hypotonic; the liver was readily palpable, but no evidence of organic disease in the abdomen or elsewhere was elicited. Her tuberculin tests were negative and x ray of the chest showed clear lung fields. When seen later after a period of two months she seemed much improved.

With a recurrence of intermittent abdominal colic and occasional vomiting in May and June, 1945, she was admitted to the Princess Beatrice Hospital where she was under observation for eight weeks. During this period no abdominal mass was palpated and no blood reported in the stools. In July, at the age of two years, the patient weighed only 17 lb. 3 oz., and difficulty was encountered in getting the child to take a solid diet, but on two occasions on examination in the out-patient department, no abnormal physical signs were found.

A final attendance in August with a recurrence of diarrhoea and vomiting, this time with blood in the stools, procured admission. Examination now revealed a sunken-eyed child, very poorly nourished, with a thickly coated tongue. The abdomen was slightly distended, while in the epigastrium a large mass, apparently in the colonic splenic flexure, was palpable. This was of rather resilient consistency, but did not alter in size after attempted colonic washouts. The rectum was ballooned and empty, while no spontaneous bowel actions were effected for three days, the lavage return being dark and containing much mucus. A barium enema was attempted but not retained.

The patient was examined under anaesthesia by Mr. Alan Small and a small lump was palpated in the left iliac fossa, of a soft consistency, and thought possibly to be an intussusception. The following day an exploratory laparotomy was performed after preparatory measures with intravenous fluids. Operation revealed a large intussusception of the terminal ileum extending as far as the sigmoid colon, with old adhesions around the entrance, and early patchy gangrene in the ascending colon. The intussusception was reducible as far as the junction of the middle and distal thirds of the transverse colon, where progress stopped and the bowel was seen to be of doubtful viability. A resection of gut was required and a side-to-side anastomosis performed.

The postoperative period was initially fairly satisfactory, aided by intravenous glucose saline, blood and plasma, but after five days signs of peritonitis were apparent. The patient's general condition rapidly deteriorated, death taking place suddenly seven days after operation.

Post-mortem examination showed that the distal stump of the transverse colon was gangrenous. There was patchy liver necrosis. Duration of the intussusception was probably one year and four months.

Case 4. A fourth case is reported in which spontaneous reduction appeared to occur on two occasions. A healthy male infant, of five and a half

months, suddenly refused feeds, had a screaming attack with legs doubled up, and vomited several times. When the infant was first examined, there was a mass palpable on the left flank. The infant was pale, apathetic, with slightly sunken eyes. On admission to hospital the same day, no mass was palpable, the infant had improved greatly in its general condition, and a saline enema produced a fairly good faecal action without blood. On the second day after admission, however, a further attack of screaming and vomiting occurred, and again a mass could be felt in the left half of the abdomen. This persisted only during the attack of pain and has apparently not returned. The stools at no time contained blood, and a barium meal and follow-through revealed no abnormality. The child has remained in good health and at the age of twelve months has had no further trouble.

Discussion

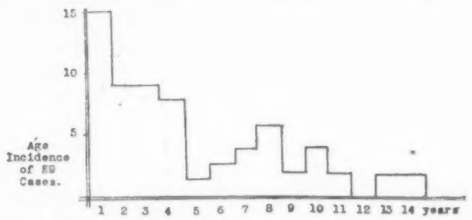
It is probable that, for an intussusception to become chronic, there must persist an abnormal or primitive type of mesenteric formation (Waugh, 1911). In place of the usual fusion of the peritoneum covering the ascending and descending portions of colon with the peritoneum of the posterior abdominal wall, there is a persistence of an ascending and descending mesocolon, and the longer these abnormal mesenteries are, the less tension there will be on the intussuscipiens and its blood supply. The gut remains viable, and congestion and bleeding are minimized until such times as increased size of the intussusception ultimately leads to signs of obstruction. The pull of the gut loaded with intussusception upon the splanchnic and renal plexuses can be provocative, Waugh stated, either of vomiting, or of pain referred to the hypogastrium and to the tip of the penis.

Sutherland (1932) observed that the passage of blood and mucus per rectum, and signs of intestinal obstruction, are often absent in cases of chronic intussusception. Of a total of sixty-nine case histories some degree of melaena on one or more occasions was present in thirty-two, rather less than half the total. Miller (1932) recorded a case of the intermittent type in a girl of three years. An abdominal tumour was present, which produced at no time any urgent symptom, and ultimately disappeared either spontaneously or aided by the bowel washouts which were given almost daily. Even with the tumour in existence, an opaque meal was almost entirely evacuated within twenty-four hours. Ten cases described by Dun (1923) illustrate the prolonged viability of the gut; symptoms were present from four weeks to two and a half years, yet at operation all were readily reducible, without adhesions, and with recovery.

Our impression is that an x-ray film of a barium enema in infants and small children in the diagnosis of chronic intussusception is seldom helpful. Screening is essential, with the buttocks held closely together to prevent escape of the enema. An opaque meal may pass fairly readily along an intussusception, until such time as its size and state of congestion produce obstruction, when the picture becomes obvious. Still (1921) recorded a case in an infant of fourteen months with duration of symptoms for six weeks, where a bismuth meal and x rays gave no assistance. Palpation under anaesthesia may be helpful, but the relaxation not only affects the muscles of the abdominal wall, but also that of the gut, whereby spasm producing a firm tumour is likely to be reduced (see case 3, compare a small soft lump felt in the left iliac fossa under anaesthesia with the extensive intussusception found at operation the following day).

The vague onset of the chronic type makes the presence of intussusception unsuspected, as 90 per cent. of the cases seen in infancy are acute (Holt and McIntosh, 1940). The symptoms are most often confused with tuberculous peritonitis and other glandular causes of intestinal colic. Repeated clinical examination is essential in order to feel a tumour, yet, in the cases we have recorded, numerous examinations were made by several observers before the nature of the illness was suspected. Laparotomy may be necessary to confirm suspicions. There can be no doubt that intermittency and spontaneous reduction of an intussusception can occur. Garvie and Kemp (1945) mention that in a series of sixty-two recorded cases a tumour was felt at some time in only forty-seven. Most importance should be attached to an analysis of the case history, the frequent repetition of short attacks of abdominal cramp, it may be over weeks, often making the child cry or double up, the poor gain, or actual loss of weight, and in many instances the presence of a negative Mantoux. Watching the progress of a barium enema by screening is the most helpful form of radiography to employ.

Though the chronic type is uncommon, the accompanying graph is intended to show the frequency with which it occurs in infancy and early childhood.



Age incidence of 59 cases of chronic intussusception.

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FIG. 1.—Scars on left buttock and thigh of case 1, two years after illness.

FIG. 2.—Isolated purpuric lesion on the shoulder of case 2.

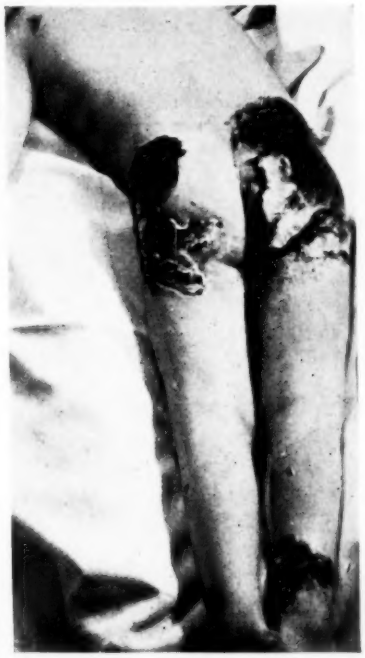

FIG. 3.—Stage of separation of the sloughs, case 2.

FIG. 4.—Scars on case 2: both buttocks and right ankle.

FIG. 5.—Scar on right buttock of case 2, taken three years after illness.

FIG. 6.—Scar on buttock of case 3.

BERI-BERI IN SINGAPORE
BY G. HARIDAS

FIG. 1.—Case apparently thriving on breast milk. A Chinese Hokkien baby, aged two months, weight 13¾ lb., was admitted for dyspnoea and cyanosis at two days. The child was fat, flabby, and very ill; the eyes rolled upwards; he was big for his age. Beri-beri symptoms were: dyspnoea, cyanosis, heart rate 128 p.m., liver markedly enlarged. Mother's knee-jerks were negative. Treatment was vitamin B_1, intramuscularly 15 mg.; vitamin B_1 tablets by mouth. Photo taken after treatment.

LYMPHOCYTIC MENINGITIS WITH LUNG INVOLVEMENT OCCURRING IN CHILDHOOD

BY

JOHN APLEY, M.D., M.R.C.P.

(From the Children's Hospital, Bristol)

Little more than twenty years ago Wallgren (1925) separated from the confused group of the meningitides those with pronounced lymphocytosis in the cerebrospinal fluid yet not due to tuberculosis or to syphilis. Since that time his 'acute aseptic meningitis' has become variously known as lymphocytic meningitis, choriomeningitis, and so on. It is considered that in approximately one-third of the cases a virus is undoubtedly implicated (Baird and Rivers, 1938), and at least three different types of virus have so far been identified.

In the past two decades the term 'atypical pneumonia' has come into common use, to cover a clinical group of infectious diseases which are similar in many respects. In a considerable proportion of cases in this group viruses are also considered to be the causative agents, and have in some instances been isolated.

Relating these two groups of diseases, both at one time euphemistically labelled 'benign,' some interesting facts have recently come to light. A virus isolated from a case of atypical pneumonia in man gave rise either to pneumonia or to meningitis in mice, according to the site of inoculation (Francis and Magill, 1938). As a corollary, the antigen developed in animals by this so-called 'meningopneumonitis' was fixed by human serum from many cases of atypical pneumonia (Rake et al., 1941). Moreover, rare cases have now been recorded in which both the nervous system and the lungs were affected by virus disease in the same patient (Scadding, 1937; Reimann, 1938; Smadel et al., 1942; Hein, 1943; Perrone and Wright, 1943). In one case the virus of lymphocytic meningitis was shown to have changed its site of election; at autopsy it was demonstrated that the lungs were affected, while the nervous system remained uninvolved (Smadel et al., 1942). There is, therefore, some relationship, albeit a rare one, between these two disease groups. The apparent rarity of involvement of both systems in a single patient may, however, be fallacious. In part it can be explained by the commonly benign course of the infections, so that revealing autopsies are exceptional; and it may be also, to some extent, an index of incompleteness of investigation. On the one hand, in atypical pneumonia symptoms suggesting the possibility of nervous involvement are notably common. Severe headache, for example, is a prominent symptom; lumbar puncture, however, is rarely performed. It is particularly in childhood that mild nervous manifestations occurring with chest disease tend to be labelled 'meningism,' and may, with improvement, be dismissed without investigation. On the other hand, in lymphocytic meningitis minor abnormal physical signs in the lungs tend to be regarded as of no significance. Atypical pneumonia is notoriously difficult to detect clinically, yet in how many instances of lymphocytic meningitis is the chest radiographed? In this connexion, perusal of eleven consecutive case reports of infants and older children who had suffered from lymphocytic meningitis revealed that abnormal physical signs in the chest had been recorded in four.

Lymphocytic meningitis is predominantly a disease of childhood. Atypical pneumonia, on the contrary, commonly affects adults. The remarkably few recorded cases in which both the nervous and respiratory symptoms have been demonstrably involved in the same patient are confined to adults; the following cases suggest a similar combination in children.

Case Reports

Case 1. D. P., ten months old, was admitted to hospital on March 7, 1946, with a history of four days' anorexia, constipation, and repeated vomiting. On the second day of the illness she had become feverish and drowsy, and a macular rash appeared all over the body, passing off by the next day. On the fourth day she developed a stiff neck; the parents became alarmed, and she was brought to hospital.

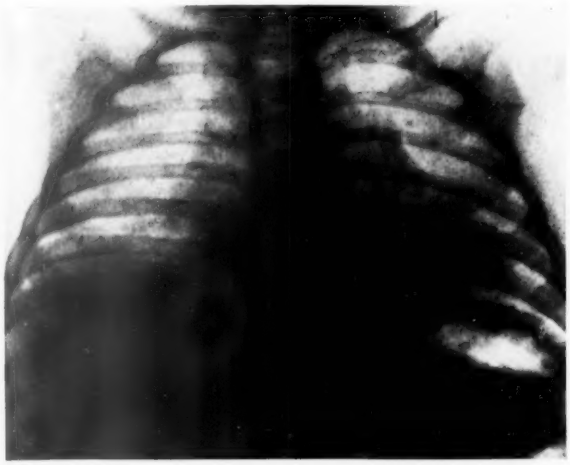

FIG. 1.—Case 1: opaque shadow at right lung base.

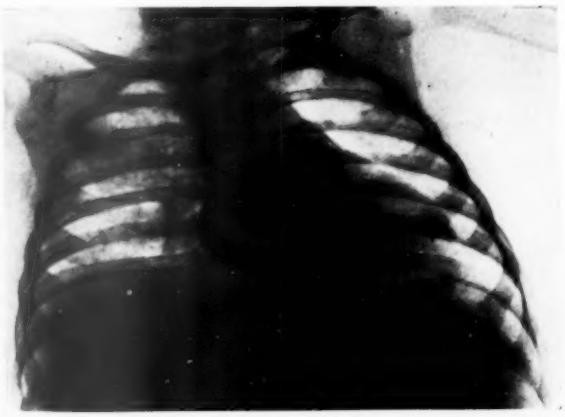

FIG. 2.—Case 1 (after thirteen days): basal shadow resolved, new area of opacity in right upper lobe.

EXAMINATION ON ADMISSION. The temperature was 103° F.

CENTRAL NERVOUS SYSTEM. Neck rigidity was marked. The spinal fluid contained 17 cells (85 per cent. lymphocytes) per c.mm., 100 mg. protein, and 680 mg. chlorides per 100 c.cm., but no organisms were seen on direct examination and culture was sterile. Nine days later the cells had increased to 50 per c.mm., almost all lymphocytes. The neck rigidity passed off in about two weeks.

RESPIRATORY SYSTEM. On admission the respiration rate was 40–45 per minute, and harsh breath sounds were audible throughout the lungs. Next day a radiograph showed a shadow at the right lung base (fig. 1). At no time was coughing a feature of the illness, and no localizing signs were elicited in the lungs, but thirteen days later a radiograph showed that the original shadow had cleared and a new one had appeared in the right upper zone (fig. 2). Three weeks later the lungs were clinically and radiologically clear. A Mantoux test (1/10,000) was negative.

The general condition remained poor for two weeks, then quickly improved. Irregular fever persisted for five weeks, after which the patient was sent home. When seen two months later she had remained well, there were no abnormal physical signs on examination, and a radiograph showed that the chest was clear.

Sulphadiazine had no appreciable effect on the disease process. The effect of penicillin was extremely doubtful; 360,000 units given during three days at the commencement of the period in hospital produced no evident change, but 960,000 units during eight days about the middle of this period coincided with a fall in temperature almost to the normal level.

Case 2. N. B., five years and ten months old, was admitted to hospital on March 11, 1946. There was a history of two weeks' cough and cold, with vomiting and fever after the first few days. A few days before admission the fever became more pronounced and was accompanied by thirst and constipation, and photophobia developed.

CENTRAL NERVOUS SYSTEM. When first seen at hospital he was drowsy and extremely irritable. Photophobia was marked, neck rigidity pronounced, and Kernig's sign positive. The spinal fluid

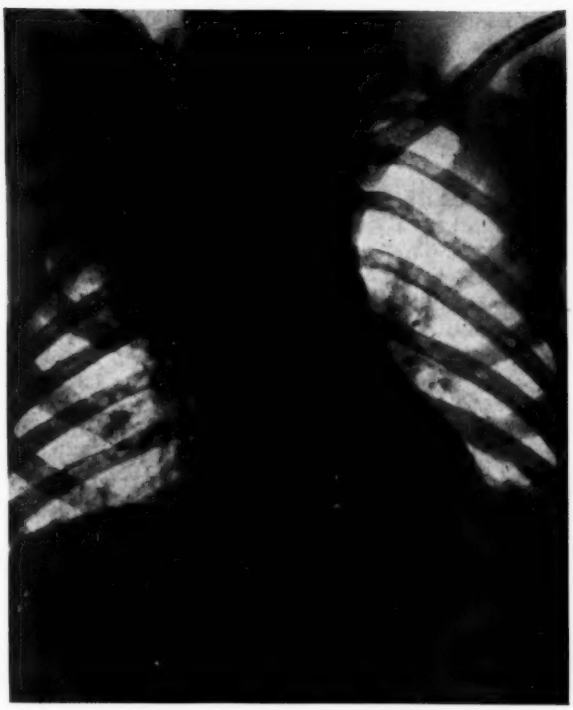

FIG. 3.—Case 2: consolidation of right upper lung and left base.

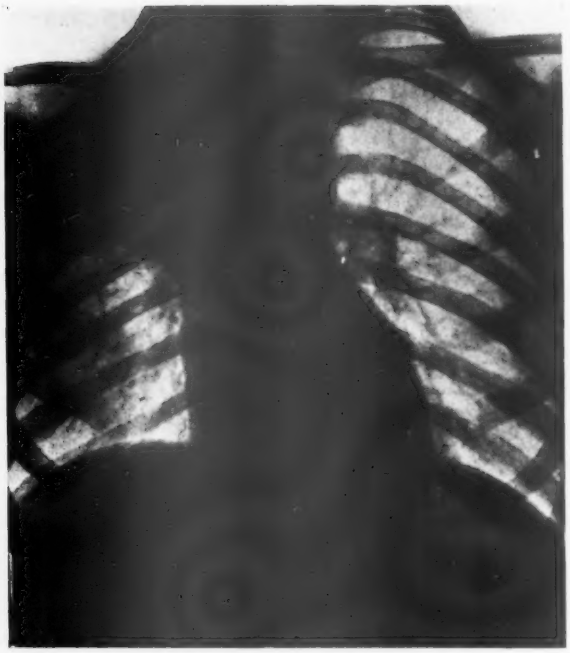

FIG. 4.--Case 2 (after five days): complete resolution at left base, consolidation and segmental collapse of right upper lung.

FIG. 5.—Case 3: enlarged left hilar shadow.

contained 26 cells per c.mm., predominantly lymphocytes, and 70 mg. protein per 100 c.cm., but no organisms were visible on direct examination, and culture was sterile. A few days later the cells had increased to 51 per c.mm., protein was 45 mg. per cent., and chlorides 720 per cent., and direct examination and culture were again non-productive. After a further eleven days the fluid contained 6 lymphocytes per c.mm., protein and chlorides were respectively 15 and 720 mg. per cent., direct examination and culture were again negative, Lange test showed 00000000000, and Wassermann reaction was negative.

RESPIRATORY SYSTEM. On admission to hospital the respiration rate was 40 per minute, and there was clinical evidence of consolidation of the right upper lung, and possibly of the extreme left base. Chest radiograph showed shadows in these regions (fig. 3). After five days the smaller of these shadows, that at the left base, had completely cleared (fig. 4), but in the right upper lung a minor degree of segmental collapse was superimposed. The shadow in the right lung gradually cleared, though even after three months a small thickened area the size of a pea was still visible in the radiograph. One month later the radiograph was completely clear. Mantoux tests to a dilution of 1/100 were negative, and sputum examination revealed no tubercle bacilli.

At the height of the illness the blood contained 14,000 cells per c.mm., of which 68 per cent. were polymorphonuclear leucocytes.

For two weeks after admission the temperature was raised four or five degrees; for a further three weeks irregular fluctuation round the 99° F. level was maintained. The respiration rate quickly fell to normal, but a mild cough persisted for several weeks. Photophobia was noted for about a month after admission, and during this period the patient vomited occasionally.

There was no evident response to sulphadiazine administered over two separate periods of several days.

Case 3. K. F., one year and eight months old, was admitted on March 13, 1946, with a history of irritability and vomiting for one week.

CENTRAL NERVOUS SYSTEM. On admission he was markedly irritable, the anterior fontanelle was patent and bulging, neck rigidity was noted, Kernig's sign was positive, and the left pupil was larger than the right, though both reacted to light and accommodation. The spinal fluid contained 350 cells per c.mm., predominantly lymphocytes, the protein content was considerably higher than 200 mg. per cent., and direct examination and culture were negative for organisms. Two weeks later the number of cells had fallen to 31 lymphocytes per c.mm., protein and chlorides were respectively 80 mg. and 700 mg. per cent., and again direct examination and culture were non-productive. Signs of meningism persisted for two weeks; bulging of the fontanelle was the last abnormal sign to disappear.

RESPIRATORY SYSTEM. The respiration rate on admission was 25 per minute. The patient had no cough, but moist sounds were audible at the left lung mid-zone. These adventitia persisted locally for a week, but repeated chest radiographs showed only enlargement of the left hilum (fig. 5). Mantoux tests were negative to a dilution of 1/1,000.

After five days in hospital the child's general condition improved, though signs of meningism persisted longer, and the temperature was slightly and irregularly raised for three weeks from the date of admission.

There was no evidence of response to sulphadiazine given over two separate periods of several days' duration.

Comment

It is a striking fact that all three cases were admitted to hospital within the space of one week, two to one hospital and the third to another. The patients were admitted from one large city, but their homes are separated from each other by a mile or more. No epidemic was prevalent at the time, and no connexion between the cases has been suggested.

General symptomatology. Persistent vomiting was an unexpected symptom common to all three patients. A macular rash, as in case 1, has been reported in similar cases (Reimann et al., 1942, and Hein, 1943), and occurs in apparently uncomplicated cases of lymphocytic meningitis.

Central nervous system. In all cases meningeal involvement was marked. The photophobia in case 2 and the pupillary changes in case 3 suggest in addition some degree of encephalitis. This is consistent with previous findings; in the few cases of lymphocytic meningitis which have come to autopsy there has been no limitation of the infection to the meninges as distinct from the brain tissue (Viets and Warren, 1937). The five weeks duration of the photophobia in case 2 is striking; the symptom itself was noted in five of eight cases reported by Reimann (1938). As compared with the majority of cases of lymphocytic meningitis, the duration of signs of meningeal involvement was unusually protacted in the three cases reported in this paper.

Respiratory system. In only one instance (case 2) was coughing a symptom. Admittedly, the remaining two patients were infants, in whom the presence or absence of cough is notoriously unreliable as a guide to respiratory infection; nevertheless the observation lends force to the suggestion that lung involvement may occur more commonly than is suspected in cases of apparently uncomplicated lymphocytic meningitis.

The time relationship between the onset of nervous and respiratory involvement is of interest, but is difficult of assessment since both systems were manifestly implicated when the patients were first examined. In case 1 both systems were involved by the fourth day of apparent illness, with no clue as to the sequence. In case 2, according to the history, infection of the lungs evidently preceded that of the nervous system. In case 3 the degree of hilar enlargement suggested pulmonary infection of some considerable duration, probably antedating that of the nervous lesion. From this incomplete evidence the possibility of simultaneous involvement of the two systems concerned cannot be excluded. In case 2 almost certainly, and in case 3 probably, it seems more reasonable to postulate primary infection of the lungs with subsequent involvement of the nervous system.

Diagnosis. The diagnosis of a lymphocytic type of meningitis seems clear. It was based on the clinical evidence of meningeal involvement, on the characteristic findings in the cerebrospinal fluid, on the lack of response to chemotherapy, and on the course of the illness.

The diagnosis of atypical pneumonia was made on the clinical and radiological findings, on the lack of response to treatment, and on the course of the disease. The coincident occurrence of lesions in two systems suggested a common pathogenesis, and tuberculosis was excluded by the repeatedly negative Mantoux responses and by the benign course of the disease. In case 1, as is common in atypical pneumonia, the radiological appearances were out of proportion to the scanty physical signs, and an additional shadow appeared as the first regressed. Characteristically, the shadows were indefinitely outlined, were comparatively lacking in density, and did not extend to the lung periphery. In case 2 the larger of the two areas of consolidation was easily demonstrable clinically in the early stages, but persisted radiologically for many weeks. In atypical pneumonia the persistence of radiographic shadows long after the patient has recovered clinically is not uncommon (Turner, 1945). In case 3 the consistent localization of the physical signs in the lung, over a period of a week of repeated examinations, indicated an inflammatory lesion of the lung parenchyma, and militated against a diagnosis of simple bronchitis. Not infrequently, the earliest radiological evidence of atypical pneumonia is an increase in the hilar shadow (Weber, 1944), and the usual sequence of extension from the hilus into the lung substance may possibly fail to develop. Nevertheless, in this single case doubt remains; but the tentative diagnosis of atypical pneumonia is advanced to emphasize the possibility of the occurrence of incomplete examples of the syndrome.

Summary

1. An account is given of virus disease producing lymphocytic meningitis and pneumonia simultaneously.

2. It is suggested that the rarity of this coincident involvement of two systems is more apparent than real.

3. The diagnosis of lymphocytic meningitis with atypical pneumonia, presumably due to virus infection, was made in three cases occurring in children.

My thanks are due to Dr. L. M. Brierley and to Dr. T. Stratton for their unstinting co-operation in the investigation of these cases. For permission to publish and for his stimulating advice and continued interest I am greatly indebted to Prof. C. Bruce Perry.

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INFANTILE BERI-BERI IN SINGAPORE DURING THE LATTER PART OF THE JAPANESE OCCUPATION

BY

G. HARIDAS, L.M.S. (Singapore), M.R.C.P.

(From the Kandang Kerbau Hospital, Singapore)

The problems presented by infantile beri-beri in Singapore during the years 1944 and 1945, up to the arrival of the liberating British forces on September 5, 1945, were of a different character from those obtaining in peace-time. They were: (a) apathy of the authorities; (b) lack of medicines; (c) lack of essential foods; and (d) shortage of milk or milk substitutes. For purpose of actual description and discussion, cases will be dealt with as they occurred among children admitted to the Japanese civilian hospital called the 'Chuo Byoin,' at Kandang Kerbau, Singapore. In pre-war days this was a maternity hospital. After Japan's declaration of war with the Allies on December 8, 1941, provision was made for the admission and treatment of casualty cases. After the fall of Singapore on February 15, 1942, the Japanese converted it into a civilian general hospital and called it the 'Chuo Byoin.' In addition to maternity beds, they provided accommodation for the treatment of adult male and female medical and surgical cases, gynaecological cases, and sick children. There were 349 beds for adults, male and female (excluding maternity beds) and 12 beds for sick children. Table 1 shows the percentage mortality in children suffering from beri-beri, compared with the total mortality for children and for adults.

Some pre-war figures of infantile beri-beri cases admitted into the Children's wards, General Hospital, Singapore, are given in table 2. The Children's wards accommodated 120 patients of under six years old. My figures during 1936 and those of Cecily D. Williams between August, 1937, and July, 1938, are as follows:

Figures of infantile mortality and of infantile beri-beri deaths respectively for the island of Singapore for the years 1938 to 1944 obtained from the Registrar-General of Births and Deaths, are given in table 3. These figures include cases treated at all Government and Municipal hospitals and dispensaries and by private practitioners. Figures between 1942 and 1945 are not very reliable, due to conditions prevailing at that time.

Population figures during the Japanese régime were unascertainable; hence comparison has to be made between the actual number of deaths of these two periods, and not between the infantile death rates.

TABLE 1

	Admissions	Deaths	Percentage mortality
Sick children ..	854	392	45·90
Infantile beri-beri	139	77	55·41
Adult in-patients	9,490	1,592	16·77

TABLE 2

		Admissions	Deaths	Percentage mortality
Infantile beri-beri	1936	316	146	46·20
	Aug. 1937 to July 1938	663	328	49·47

TABLE 3

	Infantile mortality	Infantile beri-beri
1938	5,065	25
1939	4,516	259
1940	4,819	151
1941	Not known	131
1942	7,340	97
1943	5,052	232
1944	9,039	448

Etiology

At that time the increasing incidence of beri-beri among the population showed that deficiency of vitamin B_1 constituted a serious menace to public health. Infantile beri-beri developed either: (a) in children fed on the breast milk of a woman whose diet consisted exclusively of highly milled rice or who was herself suffering from latent or manifest beri-beri (in most instances the mother appeared healthy); or (b) in children fed either on food poor in vitamins, such as highly milled rice paste, or on locally made condensed or evaporated milk introduced as substitutes for powdered milk; or (c) in children fed on cow's milk with a very low vitamin B_1 content.

Eijkman (1897), as the result of experiments on fowls, wrongly postulated that there exists in rice a toxin which produces polyneuritis and that this toxin could be neutralized by something present in the pericarp. Grijns (1901), thought that infection and intoxication played no part in the causation of this disease and that it was the result of food deficiency. Braddon (1901, 1907), Fletcher (1907), and Fraser and Stanton (1909, 1910), from investigations carried out in the Federated Malay States on the etiology of beri-beri, proved that beri-beri appears in persons who almost exclusively eat highly milled rice, and that the consumption of under-milled rice or the administration of the silvery coverings of the rice was potent not only in stopping the development of beri-beri but also in curing it. Ito (1911), observed a case of infantile beri-beri in which the mother did not have beri-beri, and called the condition ' mother's-milk intoxication.' But he afterwards changed the name to ' breast-milk intoxication ' because he saw cases in babies who were fed by wet nurses. In 1916, Segawa reported an interesting case in which nervous symptoms in a breast-fed infant disappeared when fixed feeding was given. The mother of the infant did not have beri-beri, so Segawa thought that in addition to infantile beri-beri there was another disease of infants due to breast feeding. This was the first case reported of what is now termed ' so-called breast-milk intoxication.' The nervous symptoms vanished quickly when the mother ceased to feed her baby, and reappeared when the milk of the mother was again used. Segawa concluded, therefore, that the cause of the sickness must lie in breast milk and that the malady is not the same as infantile beri-beri. Inaba (1917), insisted that, although cardiac disturbances are the most important symptoms of infantile beri-beri, the nervous manifestations of so-called breast-milk intoxication may also be seen in infantile beri-beri and are not incompatible with that diagnosis. Because of the rapidity of recovery from so-called breast-milk intoxication when patients are given vitamin B_1, Toyoda (1922) thought that the cause of the sickness was the same as that inducing infantile beri-beri.

Age

In this series of cases of infantile beri-beri, 123 were breast fed, and 14 were fed on locally made condensed or evaporated milk (see table 4). In the breast-fed group, the cases occurred with greatest frequency between the one month and four months age periods. It was also noted with less frequency in children between the seventh and eleventh months. The lowest age on record in this series was in a locally-made condensed-milk-fed infant aged seven days (case 1). The highest age on record is in a child of two years. It is included here because it happened to be breast-fed (case 2).

Infant feeding

Certain problems of infant feeding presented themselves for solution during the Japanese occupation period. Firstly there was the increased incidence of beri-beri in pregnant woman, nursing mothers, and breast-fed children owing to the consumption of an exclusive diet of highly milled rice and/or tapioca or sweet potato with no vitamin B_1 supplement. Then we were faced with the problem of providing suitable substitutes for milk when the then existing stocks of condensed milk became exhausted. There were not enough milch cows to cater for the needs of all infants who for various reasons could not be breast-fed. Even when cow's

Table 4

Age in months and days ..	7 days	1 mth.	2 mths.	3 mths.	4 mths.	5 mths.	6 mths.	7 mths.	8 mths.	9 mths.	10 mths.	11 mths.	12 mths.	24 mths.	Total
Breast-fed ..	0	27	32	16	11	7	7	2	2	6	2	0	10	1	123
Condensed milk, locally made	1	1	1	2	3	1	0	2	1	0	1	0	1	0	14
Cow's milk ..	0	0	0	1	1	0	0	0	0	0	0	0	0	0	2

milk was available, its purchase was not within the financial means of the poorer section of the population. Mothers who had too little breast milk, or those who could not obtain milk as a substitute, used to give the most easily obtainable food, that is, cooked highly milled rice, which was given in spoonfuls and was stuffed into the children's mouths in the form of a thin gruel or a rice-paste without any vitamin B_1 supplements. Among the Malays bananas were often given, both alone and mixed with highly milled rice: and in Malay children primary dietetic disturbances and infantile beri-beri were rare, the diet of rice and bananas being quite well borne. But much of the trouble resulted from the very insanitary way in which the food was stored and prepared, and from the method of administering the feeds.

Soya bean milk and sifted undermilled rice flour (or Chowbee, or bras ayam) with certain additions to make good the deficiency in fats and in vitamins A and C, were recommended as suitable substitutes for milk.

Method of preparation of soya bean milk. For one pint of milk take 2½ dessertspoonfuls of the raw beans, wash well, and soak in water overnight. Next morning pound or grind the beans (wet). Add the required amount of water and boil for 5 or 10 minutes, stirring all the time. Then strain through a thin cloth or strainer and add sugar to taste. It can be given in a bottle like milk. So that it will keep till late afternoon, it is advisable not to add sugar till the food is used, and also to keep the milk in a cool place.

Method of preparation of rice gruel as a substitute for milk. Rice gruel prepared from sifted undermilled rice flour (or Chowbee, or bras ayam), with some additions such as red palm oil and pineapple juice to make good the deficiency in vitamins A and C, was recommended as another suitable substitute for milk when the latter was not obtainable. Rice gruel made from sifted undermilled rice flour (or chowbee or bras ayam) was analysed by Rosedale (unpublished data) and was found to work out roughly at half the value of fresh milk, with the following differences: (a) gruel from sifted undermilled rice flour is rich in vitamin B_1; (b) it is notably deficient in fat and the fat is never higher than half per cent. (good milk contains at least three per cent. of fat); (c) vitamins A and C are completely absent in these gruels; (d) calcium is markedly deficient; (e) carbohydrate present is starch and not lactose. (The disadvantage of starch is that in infants under six months of age the digestion of starch is poor; but a choice between starvation, or an unsuitable starchy substitute such as undermilled rice gruel, must favour the latter.)

Method of preparation of gruel, and dosage. Take two full or heaped teaspoonfuls of the sifted rice flour, add to three ounces of water, and cook for a quarter of an hour. This forms a suitable feed for babies below four months old. From five months onwards the quantity of ground rice-flour is to be increased gradually from two to three heaped teaspoonfuls for five ounces of water. The quantity of water has to be greatly increased. From six months onwards little extras (e.g. ripe bananas, fish liver, egg, spinach, bean curd) should be added to the diet from time to time. For additional fat, it is suggested that one drachm or one teaspoonful of a mixture of one part of refined red palm oil and five parts of coconut oil be added to each of the child's feeds in the day for an infant up to one year, assuming that the infant has six or seven feeds in the day. This will greatly enhance the vitamin A value. The deficiency in vitamin C can be made up by giving the infant the juice of ripe pineapples, commencing with one teaspoonful once a day, gradually increasing this amount to one teaspoonful three times a day.

Race Distribution

Table 5 gives the race distribution of cases of beriberi. The occurrence of infantile beri-beri following the consumption of milk *per se*, or of condensed or evaporated milk produced locally, may be due to the fact that suitable fodder for cows was scarce, with the result that the vitamin B_1 content of the milk must have been low; this amount would have been still further reduced by the unsatisfactory methods employed in the manufacture of the condensed or evaporated milk.

TABLE 5

Race	Chinese	Eurasians	Indians	Total
Breast-fed ..	120	1	2	123
Locally made condensed milk ..	14	—	—	14
Cow's milk	1	—	1	2

The sale of cow's milk was not controlled by the authorities, and the following brands of cow's milk were available: (1) undiluted cow's milk at $15.00 per pau, Japanese currency (pre-war price ten cents per pau (1 pau=10 oz.)); (2) moderately diluted cow's milk at $10.00 per pau; (3) highly diluted cow's milk at $5.00 per pau. Brand 3, being the cheapest, was bought by the people for feeding their infants, and it is not surprising that infantile beriberi occurred in infants thus fed.

There were two South Indian (Tamil) cases in this series. The comparative rarity of infantile beriberi among the South Indian (Tamil) in spite of the diet of highly milled rice and/or tapioca is probably due to the consumption of other foods rich in vitamin B_1, such as ragi (Eleusine Corocona) which was cultivated to a far greater extent in Malaya than hitherto. The South Indians find ragi much more acceptable

as a food than do the Chinese. Under normal pre-war conditions, it was noted that very few cases of infantile beri-beri were encountered among the South Indians, as their staple diet consisted mainly of parboiled rice which contained a fair amount of vitamin B_1.

Economic Status

During the period under review the economic situation of the country was chaotic. Owing to the stranglehold exerted by the Allies on Japanese communications, there was an evergrowing shortage of essential foodstuffs. Inflation was marked and the purchasing value of the currency very low. Black market activities were rampant. The prices of essential foodstuffs, such as milk, eggs, meats, fish, peas, and beans, increased to an extent far beyond the reach of the average individual. Parboiled rice was not obtainable, and there were only limited stocks of undermilled rice or bras ayam or chowbee, which were sold at a high price. The rice rations per month were cut down in January, 1944, to 10, 8, and 5 lb. respectively for men, women, and children under ten years of age. In order to supplement the inadequate rice ration, sweet potatoes and/or tapioca—foodstuffs of poor nutritive value—were eaten by most people. In some instances the fathers of the infants were unemployed, in others a father with small earnings had to keep a family of five or six. Occasionally the parents were miserly in spending money on protective foods.

Dietetic History

The following is a typical economic and diet history obtained from a mother of a child with infantile beri-beri.

The mother lives with a big family, which consists of eleven persons including herself. The family owns and cultivates a piece of land, grows vegetables, rears pigs, fowls, ducks, etc. Their income is just enough to keep the farm going and to feed and clothe the family. There is little money saved. The mother's meals are: 8 a.m., kunji (rice gruel), vegetables; 1 p.m., highly milled rice, vegetables, and fish occasionally; 6 p.m., highly milled rice, vegetables, and meat (very rarely). The mother differs from the rest of the family in that she has a very poor appetite, eats little, and sometimes misses meals altogether. In some cases tapioca and/or sweet potato has to be substituted for highly milled rice. In others, kunji (rice gruel) and salt fish for one month after the birth of the child; after this rice, salted eggs, and pork (a little) comprises the diet. It is obvious that the above diets are deficient in vitamin B_1 and several other food nutrients. The circumstances leading these mothers to take these diets are either (a) poverty or (b) a belief among Chinese mothers who are breast feeding that if they partake of foods such as green vegetables, green peas, towgay, and fruits, especially during the first month of the lactation period, their infants will suffer from diarrhoea or may get wind or ' hong.'

Out of eighteen mothers examined for symptoms of beri-beri, eleven were found to be suffering from some form or other of the disease, such as palpitations, creeping sensations, numbness and tingling in the lower extremities, weakness of legs, slight oedema of ankles, tenderness of the calves with absence of knee- and ankle-jerks.

Types of Beri-beri

José Albert of Manila in 1932 drew attention to three types of infantile beri-beri: (1) the aphonic; (2) the pseudo-meningeal; and (3) the cardiac. In my series of cases the types recognized are: (1) the aphonic; (2) the peripheral neuritic; (3) the cardiac; and (4) the pseudo-meningeal. These four types may exist separately, or there may be a combination of one or more types in an individual case. The commonest form was a combination of the cardiac

TABLE 6

	Types	C.	C.: P.N.	C:A.	P.N.	A.	C.: P.N.: A.	P.M.	P.M: A.	P.M: C.	P.M: A: P.N.	P.M: P.N.	P.M: C.: P.N.	Total
Breast-fed	Cases	31	53	4	5	3	10	5	2	1	1	3	5	123
	Deaths	16	32	1	4	1	7	1	1	—	1	2	4	70
Local condensed milk	Cases	1	9	—	1	2	—	1	—	—	—	—	—	14
	Deaths	—	5	—	—	1	—	—	—	—	—	—	—	6
Cow's milk	Cases	1	—	—	—	—	—	—	—	—	—	—	1	2
	Deaths	1	—	—	—	—	—	—	—	—	—	—	—	1

Key to abbreviations: C.=Cardiac. P.N.=Peripheral Neuritic. A=Aphonic. P.M.=Pseudo-Meningeal.

and peripheral neuritic type, of which 62 cases occurred in this series (see table 6). Next in order of frequency was the pure cardiac type, with 33 cases. The pseudo-meningeal type in various combinations occurred in 19 cases. The cardiac type and its combinations gave rise to the severest symptoms and claimed the greatest number of deaths. The two deaths in the pure aphonic type were due to enteritis and bronchopneumonia respectively. In the peripheral neuritic type, deaths were due to either enteritis of bronchopneumonia.

Mortality Rate

One hundred and thirty-nine cases of infantile beri-beri, with 77 deaths, gives a percentage mortality of 55·41 per cent. This high mortality rate is due to the fact that, owing to the low stocks of vitamin B_1 existing, doses extremely inadequate to cope with the immediate acute fulminating attacks were released for use in each case by the Japanese authorities in charge. There was also a considerable time-lag factor between seeing the patient and the administration of the vitamin as, certain 'red tape' formalities had to be undergone before sanction to obtain this vitamin was permitted.

Symptomatology

The symptoms for which the infants were brought to hospital were many and varied. They included varying degrees of dyspnoea; refusing feeds, vomiting feeds, and diarrhoea; vomiting and cough, vomiting and crying continuously; constipation; no voice, husky or weak voice; inability to pass urine; inability to cry; fits; crying excessively; scanty urine; oedema of feet and legs; restlessness; flatulence; drowsiness; and convulsions. It was only after obtaining a careful history and examining the case systematically that true nature of the condition became evident.

Fever and cough were indications of the onset of respiratory-tract infection in the form of acute nasopharyngitis, bronchitis, or bronchopneumonia. These acted as exciting causes for the more urgent cardiac symptoms of infantile beri-beri. Fever and cough have been recorded for periods varying from three days up to a month before the onset of symptoms of infantile beri-beri. Other associated respiratory conditions were pulmonary oedema and congestion of the lungs.

Of the gastrointestinal symptoms, refusal of feeds, vomiting, and diarrhoea were the commonest; occasionally there was constipation or abdominal distension due to acute and persistent gaseous distension of the stomach and intestines. Refusal of feeds indicated anorexia, which, with vomiting, was the earliest symptom to appear. Vomiting varied from a small amount to the return of the whole feed, and was sometimes followed by diarrhoea. These dyspeptic symptoms might last from a few days to a month before the onset of cardiac symptoms. It is possible that this dyspepsia was, like malaria in adult cardiac beri-beri, only a common exciting cause.

Aphonia varied from slight hoarseness to complete loss of voice. It was noticed in 20 out of 139 cases. Pure aphonia was an indication of a mild attack of beri-beri, and it was found in association with the cardiac, the peripheral neuritic, and the pseudo-meningeal types. It was often persistent, and continued after all other symptoms had cleared. Direct laryngoscopy performed on a series of cases revealed that there was oedema round about the arytenoids, and it seems possible that the aphonia was due to this oedema. Wenckebach (1935) ascribes the aphonia to a paralysis of the recurrent laryngeal nerve, which at first is oedematous but later becomes permanently degenerated due to pressure from below by the dilated right heart as it slips round under the arch of the aorta.

The restlessness, fretfulness, and incessant crying in some cases may have been due to abdominal distension or to cough and dyspnoea.

The cardiovascular symptoms of infantile beri-beri are multiple. The first sign of circulatory insufficiency was persistently rapid heart rate which fluctuated with the pulse rate. Early in the disease there was slight cyanosis, mostly noticeable around the lips, and the breathing became somewhat difficult. Shortly after, dyspnoea was sometimes observed. The second pulmonic sound would become markedly accentuated and might be heard over the sternum, denoting dilatation of the right heart and increased pressure of the pulmonary circulation. The dilatation might extend considerably beyond the right sternal border, and could be demonstrated by percussion. In grave cases the heart sounds had a galloping rhythm. With further changes in the cardiac muscle the dyspnoea became more marked, the accessory muscles of respiration came into action, the alae nasi worked rapidly, and respiratory retraction of the thorax was observed. If the child cried during this stage, cyanosis was more marked and the child grunted with each respiration. During an acute attack there was extreme pallor and the voice became feeble and whispering. Frequently the infant contracted his face and mourned pitifully, as though suffering great pain, became apathetic and very soon comatose. The extremities became cold and the infant was bathed in perspiration. Sometimes there were twitchings of the extremities and the head was retracted; occasionally there might be high fever. The skin became congested and mottled, and the liver much enlarged. Dyspnoea became more and more severe, and death ensued.

Oedema was generally slight or moderate, and appeared chiefly on the face and extremities. It often occurred in association with diminution of urine.

Listlessness and limpness of the limbs were noticed and the child 'would not play.' Pseudo-meningeal symptoms varying from mild twitchings of limbs to violent convulsive movements. Sometimes there was rigidity of the neck with tenseness of the anterior fontanelle. The infant grew either drowsy or unconscious. Lumbar puncture revealed a cerebrospinal fluid that came out under increased pressure and was clear, with practically no increase in cells or albumin. Knee-jerks and ankle-jerks were absent if there was a peripheral neuritis. In the present series there were nineteen cases with ten deaths, giving a mortality of 52·16 per cent. Urinary symptoms varied from diminution in the amount of urine passed to almost complete suppression.

Physical Examination

The patients in this series can be divided into two groups.

The first group of children appeared to be well nourished but were a little pale and flabby. There was sometimes slight duskiness about the lips which could be detected only by careful observation. The child was usually brought to the out-patient department because of listlessness, limpness of the limbs, huskiness, breathlessness, or because it would not play. The heart rate was usually rapid, the liver enlarged; and the knee- and ankle-jerks might or might not be absent. This group of children apparently thriving on breast milk, were suffering from the effects of vitamin B_1 deficiency (see fig. 1, p. 17).

The second group of children, in addition to suffering from the effects of a lack of vitamin B_1 in breast milk, were also not thriving on it. They showed marked pallor and were undernourished. Slight puffiness of the face and slight oedema of the hands and feet were present. They were restless, breathed rapidly with little or no sound, the feeds were returned, and there might be severe vomiting. There was sometimes a weak cough with no physical signs in the lungs. The heart beat was fast, weak, and regular, usually with no murmurs. The knee- and ankle-jerks were absent.

A careful inquiry into the health of the mother during pregnancy, and particularly into her diet during the last month of pregnancy and during lactation, should be made in every case to determine whether she received an adequate diet. It is necessary to bear in mind that an infant can have his knee- and ankle-jerks present and yet suffer from beri-beri. This has been proved by post-mortem examinations on cases whose knee- and ankle-jerks were present and who died of an acute cardiac attack. The type of case that presents difficulty in diagnosis is the case with only one symptom, like hoarseness of voice. If the knee- and ankle-jerks are present, then the presence of tachycardia, dilated heart, and enlarged liver with evidences of circulatory failure, coupled with a history of breast-feeding on a vitamin B_1 deficient diet, will make the diagnosis easy. If there is no history of breast-feeding and the infant is fed on locally made condensed milk or on a dilution of cow's milk and is suffering from aphonia, diagnosis is a little more difficult. It has to be made by a process of exclusion and by a therapeutic test, that is, improvement with parenteral administration of vitamin B_1.

Illustrative Case Reports

CASE 1. The youngest case in the series. A Chinese Teochew male infant, aged seven days, was brought to hospital on May 25, 1944. No history was obtainable as the mother was ill at home. The infant was fed on condensed milk. On admission the infant was poorly nourished and dyspnoeic. He had a temperature of 99·5° F. and the pulse and heart rates were rapid. The cord had dropped off the umbilicus and there was no sepsis. The knee-jerks were absent. Only 1 mg. of vitamin B_1 was available for parenteral administration. The infant died the next day. This was a case of infantile beri-beri of the cardiac and peripheral neuritic type.

CASE 2. The oldest case in the series. A Chinese Cantonese female child, aged two years, was brought to hospital on June 19, 1944, with a history of diarrhoea, vomiting, fever, and slight cough for four days. The child was breast-fed. On examination, the child was febrile, the extremities were cold, and she was dehydrated and moribund. There was some cyanosis and congestive mottling of the skin. The heart was rapid and there were few crepitations in the lungs. The liver was little larger than normal, and knee- and ankle-jerks were not elicited. A diagnosis of gastro-enteritis and infantile beri-beri of the cardiac and peripheral neuritic types was established. The child died six hours after admission. No vitamin B_1 was available for treatment.

The following case report is that of a case not included in the series.

A Chinese Hokkien female breast-fed infant, aged five months, was admitted to hospital with a history of loss of appetite. The mother was suffering from herpes zoster over the right side of the chest, and she had ceased breast-feeding four days before admission. The infant was found to be pale, undernourished, cyanosed, and dyspnoeic, with a feeble cry. There was a rise of temperature, and the heart rate was rapid. The lungs were full of moist sounds. The liver was larger than normal. The knee- and ankle-jerks were absent. A diagnosis of infantile beri-beri of the cardiac, aphonic, and peripheral neuritic types with associated lung infection was made. The general condition of the infant at that

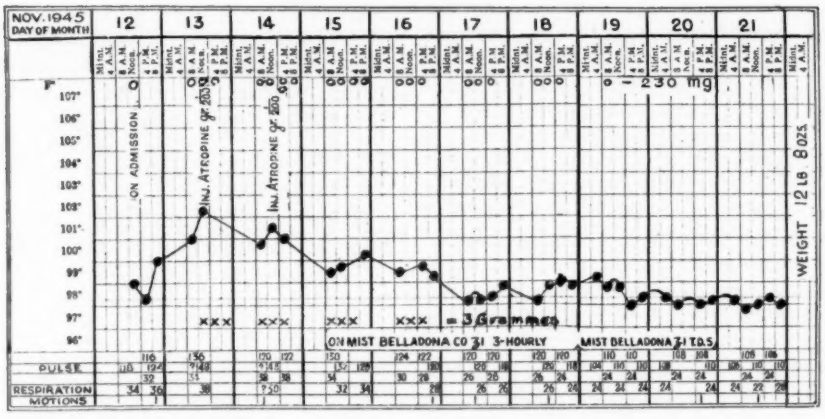

FIG. 2. Temperature chart of a child aged five months, receiving sulphonamide-P and injections of vitamin B_1. X=sulphonamide, 0·25g. O=injections of vitamin B_1, 10 mg. intramuscularly.

time was so grave the vigorous anti-beri-beri treatment and treatment to control the lung infection was instituted immediately. Altogether, within a period of six days, 230 mg. of vitamin B_1 intramuscularly, and 3 g. of sulphonamide-P by mouth were administered (see temperature chart, fig 2). At the end of this period, there was no cyanosis and no dyspnoea. The colour of the infant had improved. Its lips and tongue were pink. The heart sounds were not so rapid, and there were only coarse rhonchi in the lungs. The liver had diminished in size. The knee- and ankle-jerks had returned. The infant was quite hungry and finished all its feeds. The feeble voice took about six weeks to improve. For treatment, the infant had 230 mg. of vitamin B_1 intramuscularly, two injections of atropine sulphate gr. $\frac{1}{200}$ each, sulphonamide 3 g., and belladonna mixture.

Differential Diagnosis

The following diseases have to be distinguished from infantile beri-beri: (1) idiopathic cardiac hypertrophy; (2) improper feeding and indigestion; (3) congenital heart disease; (4) respiratory diseases; (5) infantile muscular atrophy of spinal origin; (6) diffuse poliomyelitis; (7) diphtheritic paralysis; (8) nephritis; (9) meningitis; (10) laryngeal diphtheria; (11) laryngitis of measles.

1. A patient suffering form idiopathic cardiac hypertrophy, has to be distinguished from an infant with the cardiac condition in beri-beri. There is a striking clinical similarity in the two conditions, but a history of vitamin B_1 deficiency in the beri-beri infant's mother's diet will help to differentiate these conditions. On post-mortem examination the right ventricle of the heart is most seriously involved in beri-beri, while in idiopathic hypertrophy both sides of the heart are attacked, the hypertrophy and dilatation of left ventricle predominating. If there is no history of breast-feeding, then the possibility of a clinical syndrome fitting in with the description of infantile beri-beri in a locally-made condensed-milk-fed baby should be considered. A therapeutic test should be applied to settle the diagnosis. A case of infantile beri-beri will improve with vitamin B_1 injections.

2. Failure of the infant to gain weight on the breast, with some colic, restlessness, and constant crying, may occur in an underfed infant; and the grosser symptoms of indigestion, such as vomiting, colic, and diarrhoea may be due to overfeeding or to infection in a breast-fed infant and yet the infant may not be suffering from infantile beri-beri. These symptoms may exist in association with infantile beri-beri or act as a common exciting cause of the syndrome.

3. The diagnosis of cyanosis and dyspnoea of congenital heart disease will be confirmed by (a) the presence of a murmur and its location (b) the presence of clubbing of the fingers and toes in some cases (c) a history of cyanosis from birth. A dilatation of the right side of the heart and an enlarged liver are present in congenital heart disease and in infantile beri-beri. In the latter condition a history of breast-feeding on a vitamin B_1 deficient diet will be obtained.

4. In cyanosis and dyspnoea of respiratory origin which may be due to laryngeal, tracheal, or bronchial obstruction, bronchitis, bronchopneumonia, or atelectasis, the history and the presence of physical signs in the chest will make the diagnosis clear. Differentiation may be difficult in a case where bronchopneumonia occurs as a terminal event in beri-beri. Here again the history will be helpful in suspecting the condition.

5. Infantile muscular atrophy of spinal origin which occurs in an infant in the first weeks or months of life and where the infant develops a flaccid paralysis of all the extremities will not present much difficulty in diagnosis.

6 and 7. Diffuse poliomyelitis and diphtheritic paralysis have to be differentiated from infantile beri-beri with neuritic symptoms In diffuse poliomyelitis, the paralysis and atrophy of muscles is rarely symmetrical and groups of muscles tend to be affected. In a case of diphtheritic paralysis, in addition to the incomplete paralysis of the limbs, the eyes and palatal and laryngeal muscles are affected and the diaphragm is weak. In infantile beri-beri, as opposed to these two conditions, there is no definite paralysis and the neuritis of the lower limbs is symmetrical.

8. A case of oedema from nephritis can be distinguished from infantile beri-beri with oedema by the presence of albumin in the urine.

9. Children admitted into hospital for convulsions due to beri-beri may have to be distinguished from those with convulsions due to meningitis by the absence of other symptoms of meningitis, such as bulging and tenseness of the anterior fontanelle, arching of the back and neck, internal squint, and exaggerated reflexes. In meningitis, lumbar puncture will reveal an abnormal cerebrospinal fluid. The convulsions in beri-beri have improved after treatment with vitamin B_1 and have not been known to recur.

10 and 11. The aphonic type will have to be differentiated from laryngeal diphtheria and laryngitis occurring at the onset of an attack of measles. In laryngeal diphtheria, careful examination of the throat will reveal a patch of membrane in an exposed situation, and from the throat swab the diphtheria bacillus will be cultured. The laryngitis occurring at the onset of an attack of measles may give rise to doubt as to diagnosis. But the presence of pyrexia and the discovery of Koplik's spots on the buccal mucosa will solve the problem.

The importance of giving an injection of 10 mg. of vitamin B_1 when in doubt about the diagnosis must be emphasized. An improvement in the symptoms will be noticed if it is a case of infantile beri-beri.

Post-mortem Findings

The following is a verbatim description given by Tull, quoted by Wenckebach (1935): 'The interior of the thorax was a really wonderful sight, the right heart extending greatly to the right, the surface shining, the vessels under the pericardium much engorged and the right ventricle dilated to almost breaking point. The pulmonary artery was the same size as the aorta. The heart was as large as that of a normal child ten years old.' In the same case 'the liver was much enlarged and the wall of the gall-bladder typically oedematous; there was complete absence of oedema of lungs.' In the present series of cases there were a number with oedema of the lungs, some with congestion of the lungs and bronchopneumonia. In the nervous system there was marked engorgement of the cerebral blood vessels. There was a small amount of effusion in the pericardial sac and in the abdominal cavity.

Prognosis

In the aphonic type it takes about six weeks for the voice to recover.

In the pseudo-meningeal type, without complications, the prognosis is good provided adequate doses of vitamin B_1 are administered parenterally. If there is a rise of temperature, malarial infection must be excluded by an examination of the blood-film. During an attack of convulsions, the throat must be cleared to prevent death from suffocation.

In the cardiac type, cold, clammy hands and feet are signs of grave circulatory failure. Therefore, in such cases, treatment for restoration of circulation should be energetic because it is absolutely essential to keep the heart going until such time as vitamin B_1 injections take effect. Very often cases are brought into hospital where the circulatory failure is so severe that the infant dies before anything can be done for its restoration.

The old idea that a beri-beri heart is permanently damaged does not hold good, provided adequate doses of vitamin B_1 are administered during the acute stage. A follow-up of cases of acute beri-beri that have recovered shows that, given the same chances as a normal infant in regard to diet and care, the former invariably grow up to be healthy and strong.

In certain cases, an acute cardiac attack supervenes upon a subacute cardiac condition which had been undiagnosed for a long period. In such cases there is considerable oedema of the heart muscles, and thus they fail to recover even after an injection of 60 to 80 mg. of vitamin B_1.

Expiratory grunt is an unmistakable sign of an acute cardiac attack. This sign can be recognized from a great distance. Anxious parents often ask, 'When will the infant be out of danger?' It is possible to say that the vitamin B_1 injection will take at least one and a half to two hours to have effect, and that, if the infant's heart will respond to the drug, it should recover. It takes about one and a half to one and three-quarter hours for the grunt to cease in favourable cases. In cases that are going to end unfavourably, the grunt ceases rather early, that is, within a period of about three-quarters to one hour after the vitamin B_1 administration. The infant's respiratory system often gets choked with secretion, the heart sounds become feeble, and it dies.

Numerous fine crepitations at both bases, and bronchial breath sounds are associated with grave prognosis. Some cases which get cured rapidly in

twenty-four hours, and are sent home, are brought back at the end of the second day with signs of acute bronchitis developing rapidly into acute bronchopneumonia. The cause of this is probably either (a) associated avitaminosis A and D predisposing to respiratory tract infection, or (b) inhalation of infected mucus during the acute stage. In such cases it is advisable to administer sulphonamide-P as a measure of prophylaxis if the temperature rises on the second day.

Treatment

The treatment of infantile beri-beri can be divided into: (1) treatment of the mother; (2) treatment of the infant.

Treatment of the mother consists in attention to her health and diet during pregnancy and during the lactation period. As parboiled or undermilled rice was not obtainable, overmilled rice and/or tapioca or sweet potato had to be taken. Tapioca, sweet potato, and overmilled rice contain small amounts of vitamin B_1. In the process of milling the rice, the vitamin B_1 which is found in the husk and outer layers of the grain is removed. The very valuable mineral salts are also removed with the husk. As, through ignorance, the public do not supplement the diet with vitamin B_1, hypovitaminosis B_1 results. The consumption of an exclusive diet of overmilled rice is harmful, because the high carbohydrate diet will require a correspondingly high ingestion of vitamin-B_1-containing foods. Good sources of vitamin B_1 are soya bean, green dhall, peanut, rice polishings, husked rice, hen egg, duck egg, and salted duck egg.

The data in table 7 have been obtained from Leong (1940), who did a fairly complete assay of the B_1 content of foods obtainable in Malaya. Because of the peculiar belief that green dhall, green vegetable, and bean sprouts will give rise to wind or ' hong ' in the mother and green diarrhoea in the infant, it is difficult to make the mothers take these foods. The mothers were warned of the dangers of abstention from these valuable foods. If the mothers refused to take them in spite of advice, weekly or fortnightly intramuscular injections of vitamin B_1 or tablets of this vitamin were given. The mother should be examined for signs and symptoms of vitamin B_1 deficiency, such as creeping sensations, numbness and tingling in the lower extremities, weakness of legs and slight oedema of the ankles, tenderness of calves with absence of knee- and ankle-jerks.

The most dangerous feature of infantile beri-beri is that the mother does not realize the gravity of the disease in her infant until alarming symptoms develop. We always advocate that all infants from poor families should be brought to the out-patient department for attention and advice. The medical officer could detect the symptoms of beri-beri in its early stages and give suitable advice and treatment.

Before the introduction of vitamin B_1 for parenteral administration, treament of the baby consisted of (1) weaning the infant from the breast and administering condensed milk feeds; (2) giving brewer's yeast powder or Marmite; (3) administering cardiac stimulants in cardiac failure, and oxygen for the cyanosis. This line of treatment proved unsatisfactory. Since the introduction of potent vitamin B_1 preparations, we have been able to introduce systematic treatment. If the case belongs to the group which has been described previously as

TABLE 7

VITAMIN B_1 CONTENT OF FOODS

English name	Scientific name	Local name	International Units per 100 g.
Soya bean	Glycine hispida	Kachang Soya	240
Soya bean curd	,, ,,	Tauhu	11
Soya bean curd (hardened)	,, ,,	Towkua	43
Soya bean milk	,, ,,	—	8
Green dhall	Phaseolus radiatus	Kachang hijau	270
Peanut	Arachis hypogea	Kachang goreng	235 (baked)
Rice polishings	—	Dedak	600–800
Husked rice	Oryza sativa	Bras ayam	140
Bean sprouts	Phaseolus radiatus	Taugeh	13 (fried)
Sweet potato	Ipomoea batatas	Keledek	28 (boiled)
Tapioca	Manihotutillissima	Ubi kayu	19 (boiled)
Milk, fresh cow's	—	Susu lembu	3
Hen egg, yolk	—	Telor ayam	110-270 (boiled)
Duck egg, yolk	—	Telor itek	200–375 (boiled)
Salted duck egg, yolk ..	—	Telok asin	210–440 (boiled)

thriving on breast milk but which is only manifesting symptoms of vitamin B_1 deficiency, the treatment is as follows: (1) breast-feeding is continued; (2) the mother is put on an anti-beri-beri diet consisting of husked rice or 'bras ayam' four ounces, soya bean curd or 'tauhu' four ounces; green vegetables four ounces; bean sprouts or 'taugeh' four ounces; green dhall two ounces; (3) she is given 10 mg. vitamin B_1 daily for six days, and this treatment is discontinued when once the symptoms in the child have improved; (4) the infant is given intramuscular or intravenous injections of vitamin B_1, the amount depending upon the severity of the case; (5) after discharge, the mother is instructed to follow a dietetic regimen similar to the one she had been taking in the ward, and to attend the outpatient department weekly.

Vitamin B_1 preparations have been put out for use in two forms, tablets for oral administration and solutions for parenteral administration, expressed in milligrammes (1 mg.=333 international units). For rapid effect, vitamin B_1 should be administered in large doses either intravenously or intracardiacally. It is excreted rapidly, and no toxic effects had been noted in my series of cases.

For intravenous administration, the superior longitudinal sinus through the anterior fontanelle is chosen. About 7 c.cm. of blood is withdrawn as a measure of venesection, and through the same needle 10 mg. of vitamin B_1 is injected. If there is no improvement within an hour, the injection is repeated. In addition, intramuscular injections of vitamin B_1 should be administered in 10 mg. doses. It is never safe to give less than 10 mg. as an initial dose. If, as occasionally happens, intravenous administration is unsuccessful, intracardiac injections must be given as a final resort. The disadvantage of this method is that the needle may not reach the heart, and if it does reach the heart there is considerable bruising of the myocardium, as has been demonstrated at autopsy on a few cases that have died.

The total dosage depends upon the severity of the case. In the milder cases about 20 to 25 mg., and in the more severe cases 60 to 70 mg. may be necessary before improvement in the condition is noted. The results of vitamin B_1 injection in cases that are improving are: (1) cyanosis lessens and disappears eventually; (2) dyspnoea improves; (3) the infant's colour improves; from the dusky colour of cyanosis, he becomes pink; (4) if he has been restless before, he now lies quietly in bed; (5) the rate of the heart slows down; (6) vomiting disappears; (7) the knee- and ankle-jerks return in some cases where they have been absent before.

Symptomatic treatment consists of: (1) for persistent abdominal distension, flatus tube, rectal wash-out, and pituitrin $\frac{1}{4}$ c.cm.; (2) injection of atropine sulphate, gr. $\frac{1}{300}$, for moist sounds in the lungs; (3) bromide and chloral for convulsions; (4) O_2 for the cyanosis; (5) treatment for rapid restoration of circulation as follows: (a) brandy to be rubbed on the lips; (b) brandy ℥ss v in a teaspoonful of water to be given by mouth four-hourly; (c) one tablet of vitamin B_1 (1–2 mg.) with one drachm of carminative mixture for infants to be given half-hourly till improvement is noticed; (6) hot water bottles to be applied to limbs and sides of trunk; (7) do not push fluids too rapidly because the stomach will become distended and the infant will vomit with regurgitation of fluid into the lungs.

In dealing with the type that is not thriving on breast milk or where the mother is suffering from beri-beri, the infant is weaned and is given a suitable substitute feed to make good the vitamin deficiencies. The rest of the treatment is the same as that outlined for the type that is apparently thriving on breast milk.

If a breast-fed infant is brought to hospital for treatment of a complaint other then beri-beri, it is always advisable to administer a prophylatic dose of vitamin B_1 intramuscularly, say 5 mg., because a number of such children have collapsed suddenly and have died. Autopsy revealed the cause of death to be infantile beri-beri.

Summary

1. Infantile beri-beri is B_1 avitaminosis.

2. In Singapore during the latter part of the Japanese occupation it occurred in breast-fed, locally made condensed-milk-fed and very occasionally in cow's-milk-fed infants.

3. It occurred in four forms: (a) aphonic; (b) peripheral neuritic; (c) acute cardiac; (d) pseudo-meningeal.

4. The clinical signs indicating a cardiac attack are dyspnoea, cyanosis, tachycardia, dilatation of the right side of the heart, accentuation of the pulmonary second sound, and enlarged liver, and in extreme cases a congestive mottling of the skin.

5. It is not common in infants who are breast-fed by mothers who are poor and who eat unmilled rice.

6. It is common in the poor who eat highly milled rice.

7. An absence of knee- and ankle-jerks is not essential for the diagnosis. It may be purely a cardiac affection.

8. Vitamin B_1 solutions administered parenterally have proved satisfactory in the treatment of this condition.

9. It is never safe to give less than 10 mg. as an initial dose.

10. The diet of the nursing mother determines the condition of her milk.

11. The symptoms of vitamin B_1 deficiency in the mother are palpitations, creeping sensations, numbness and tingling in the lower extremities, weakness

of legs, slight oedema of ankles, and tenderness of calves with absence of knee- and ankle-jerks.

Summary of Difficulties and New Features seen in Infantile Beri-beri during the Japanese Occupation Period.

1. Difficulty in getting vitamin B_1 in adequate amounts to save a case.

2. The prohibitive price, 10 mg. of locally prepared vitamin B_1 costing $250.00 Japanese currency, and 10 mg. of foreign-prepared vitamin B_1 costing between $600.00 to $700.00 Japanese currency.

3. Secondary infections: frequency of lung complications, especially bronchopneumonia, after apparently efficient treatment. This was not seen in pre-war days.

4. Associated avitaminosis A, B, and D: more common in locally made condensed-milk-fed babies and probably also accounting for the secondary infection. Such children are pale and thin with subrickety manifestations.

5. Cardiac collapse is more severe.

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(*For Photographic Illustration of this Article see page 17*)

COLD SWEATING, HYPOGLYCAEMIA, AND CARBOHYDRATE INSUFFICIENCY

WITH PARTICULAR REFERENCE TO COELIAC DISEASE

BY

J. L. EMERY, M.B., Ch.B., D.C.H.

(From the Department of Pathology, University of Bristol)

That sweating is an exceedingly common phenomenon in ill children can be attested by any nurse or paediatrician. Much of this sweating is associated with pyrexia, but there are many disorders, particularly those of nutrition, in which a rise of temperature is not common and which have been classically linked with sweating e.g. rickets, prematurity, and pink disease. Cold sweating may be defined as sweating which occurs without an adequate thermal stimulus (Hemingway, 1944), thus excluding sweating due to cold stimuli (Kuno, 1934).

The possible clinical importance of cold sweating in children was suggested during investigations on insulin tolerance in children with coeliac disease. Nurses spontaneously remarked that the symptoms which were demonstrated to them as being due to insulin hypoglycaemia were of common occurrence in such patients and in other wasted ill children, occurring mostly during the night.

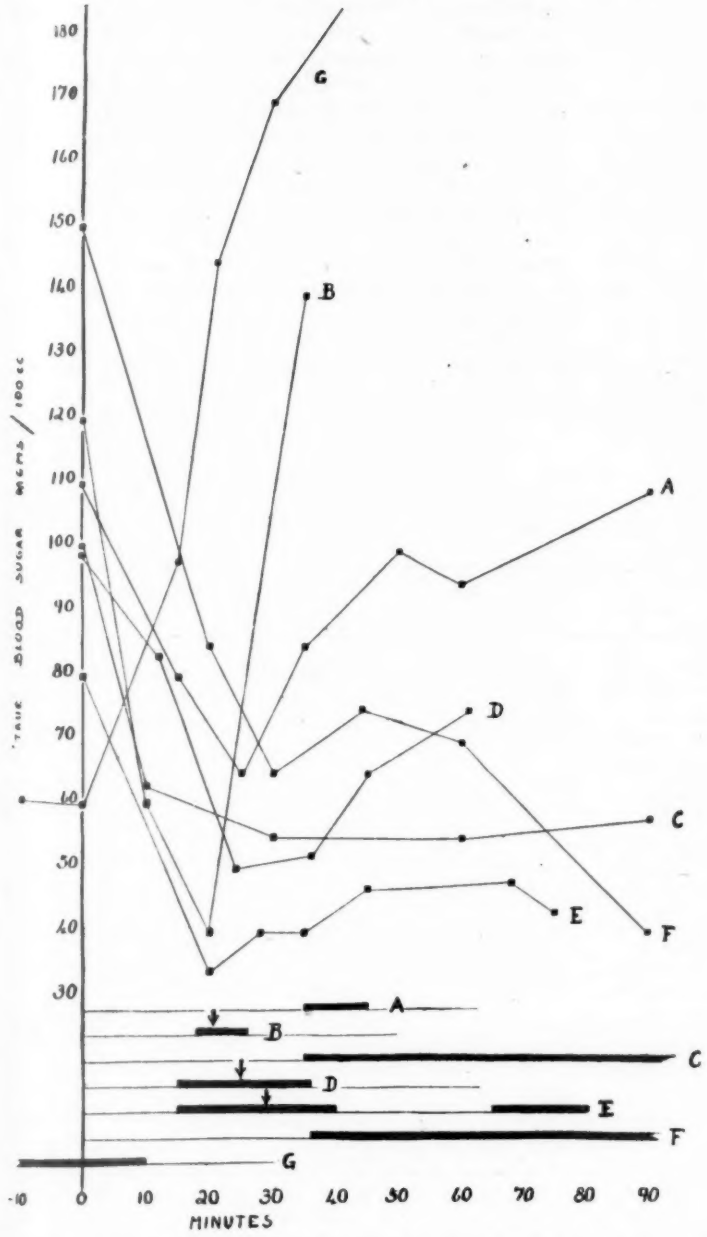
The relationship of cold sweating to hypoglycaemia is well recognized (Frostig, 1938; Himwich, et al., 1939). Himwich (1944) includes it in the first, and Wauchope (1933) in the second phase of progressive hypoglycaemia. By most it is assumed that the sweating is due to the adrenaline produced in the response to the hypoglycaemia (Cannon et al., 1924). Adrenaline usually does not produce sweating in man, sweat glands being cholinergic. In clinical association with cold sweating many other symptoms related to hypoglycaemia have been described e.g. colic (Quigley et al., 1929), and symptoms simulating appendicitis (Sandler, 1941; Brown, 1944). Further, the blood-sugar level at which symptoms of hypoglycaemia occur seems to be remarkably inconstant (Wauchope, 1933) even when allowance has been made for varying techniques and personal factors in observation.

Sweating is an easily recognized symptom and thus its relationship to the blood-sugar and carbohydrate metabolism is of some clinical importance. This paper records investigations of this relationship.

Clinical material. Three groups of children have been investigated: (a) seventeen normal convalescents; (b) thirteen children with coeliac disease, in which it has been shown that there is a state of carbohydrate insufficiency; and (c) three diabetics, who have a carbohydrate disorder. In each of these groups the relation of the cold sweating to the blood-sugar level has been observed in the hypoglycaemic period following the intravenous injection of insulin, and following the oral administration of glucose and intramuscular adrenaline. The relation of sweating to the intervals between meals was observed; the blood sugar estimated, and also the relative fasting sugar levels in the patients with coeliac disease and controls. The observations here reported have been confined to sweating for, although there were often other symptoms, sweating is by far the most constant early symptom of hypoglycaemia and the most easily noted; other changes such as pallor, dilatation of the pupil, and blood pressure changes, are difficult to assess and involve disturbing a sleeping child.

Technique. Details of the techniques used in the biochemical tests have been given in a previous paper (Emery, 1946), drug dosage being related to body weight (glucose 1 g. per kg., adrenaline 0·001 g. per kg., insulin 0·1 unit per kg.). The method of blood-sugar estimation used, that of Folin and Wu, records the reducing capacity of a protein-free filtrate of the blood, and the figures quoted in this paper have been corrected for true blood-sugar level (Herbert and Bourne, 1931). For convenience of record the degree of sweating was given arbitrary numerical values, the skin texture being estimated with a cool, dry hand:

(0) skin of normal dry consistency;
(1) skin moist in folds e.g. in palms or behind ears;
(2) skin slightly moist all over;



Curve A = intravenous insulin tolerance test on a normal child.

Curve B = intravenous insulin test on a normal child in which adrenaline was given intramuscularly at the point marked by the arrow.

Curve C = intravenous insulin tolerance test on a child with the coeliac syndrome.

Curve D = intravenous insulin test on a child with the coeliac syndrome in which glucose (1 g./kg) was given at the point indicated by the arrow.

Curve E = intravenous insulin tolerance test on a child with the coeliac syndrome in which adrenaline was given intramuscularly at the point indicated by the arrow.

Curve F = intravenous insulin tolerance test on a diabetic child well controlled by insulin.

Curve G = a combined intramuscular adrenaline and oral glucose test on a coeliac patient who was cold sweating after fasting for four hours. The administration took place at 0 minutes.

FIG. 1.—Showing, in sample cases, the relationship of the blood-sugar level to cold sweating in time. Sweating is indicated by the thick blocked-in line at the base of the chart, the letters indicating to which curve each refers. Sweating is of category 2 (see text under technique) or over.

(3) roots of hair wet, particularly behind the ears;

(4) frank sweating, e.g. beads of sweat on brow, pillow damp, hair wet, etc.

Emphasis was laid on the head, as this is the only part of the body consistently available in the sleeping child without disturbing sleep. The numbers given to the sweating categories are for convenience, and it is not suggested that category 4 indicates twice the sweating of category 2. In all cases when sweating is mentioned cold sweating is indicated, no child being used who during the test or for the two previous days had shown a rise in temperature or an increase in pulse rate.

Results

SWEATING FOLLOWING INTRAVENOUS INSULIN IN NORMAL CASES

Following the intravenous injection of insulin in eleven normal children, six showed abnormal signs, including sweating. The maximal fall in blood sugar occurred in all cases by twenty-five minutes after the injection, and was followed then by a fairly rapid return to normal. In all but one case the blood sugar was below 70 mg. per 100 c.cm. of blood (the generally accepted hypoglycaemic level) in ten minutes. The mean onset of sweating occurred at thirty-five minutes, in three cases there being no symptoms until after forty minutes. Thus there was a lag of between ten and twenty minutes between the blood sugar reaching a 'hypoglycaemic' level and the onset of symptoms. Symptoms with sweating lasted ten to thirty-five minutes. This led to the situation that between fifty and sixty minutes after the injection, in all cases with sweating, the blood sugar had returned to within 30 mg. per 100 c.cm. of the resting level, and during the same time five of the six cases were still sweating (fig. 1, curve A). In one case (fig. 1, curve B) the onset of symptoms was exceptionally early, but the blood sugar had been below 60 mg. per 100 c.cm. for the eight minutes preceding the onset of symptoms. This child was then given an injection of adrenaline. The cases in which sweating occurred were not those showing the lowest levels of blood sugar; one case showing a fall of 65 mg. per 100 c.cm. from the resting level showed no symptoms.

It is thus demonstrated that cold sweating may

TABLE 1

GIVING THE RELATIONSHIP OF SWEATING TO INTERVALS BETWEEN MEALS IN SEVEN COELIACS AND SEVEN OTHER CHILDREN IN ADJACENT BEDS

The numbers refer to categories of skin texture described in the text under technique; (a) indicates awake and demanding food. The meals indicated consisted, in the coeliacs, of the usual fat low, high protein, diet and in the controls of normal hospital diet.

		Tea			Supper			Milk Drink										Milk Drink	Breakfast	Drink			Dinner		
		Noon			p.m.							midnight						a.m.							
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Coeliacs	1	1	0	0	0	0	0	0	0	3	4a	3	3	4a	3	3	3	1	0	0	0	1	1	0	0a
	2	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	1	0	4a	1	0	0	0	0	0
	3	1	0	0	0	0	0	0	0	1	4a	1	1	1	1	0	1	0	4a	1	0	0	1	0	0
	4	2	2	1	1	1	1	1	1	4	4	4	4	4	4a	3	4	2	1	1	1	4a	2	4a	0
	5	1	1	0	0	0	0	1	1	0	0	0	3	3	1	1	2	1	0	0	0	1	0	1	0
	6	1	1	0	0	0	0	1	1	0	0	0	0	0	4a	0	0	0	0	0	2	0	1	1	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	0	0	0	0	1	0	0	0
Coeliac Total		6	4	1	1	1	1	3	3	8	13	9	12	13	14	9	13	4	9	3	3	7	5	6	0
Controls	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0
	2	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	1
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	4	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
	5	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
	7	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	1	0	1	0	0	1	0	0
Control Total		2	0	0	2	2	0	1	1	1	1	2	3	2	2	3	5	1	0	1	0	1	4	2	2

occur in normal children associated with insulin hypoglycaemia, there being a lag period of between ten and twenty minutes before the onset of symptoms after the blood sugar has fallen, which, in cases showing a normal rapid hypoglycaemic response, makes the symptoms coincide with the recovery phase or even follow it.

Sweating following the intravenous injection of insulin in diabetics

Insulin in standard dosage was injected repeatedly in two cases of juvenile diabetes, during experiments on the effect of fat intake upon insulin sensitivity in children. In no instance in these diabetics did sweating occur although the blood sugar fell rapidly, but the blood-sugar level was high (over 300 mg. per 100 c.cm. of blood), the depression produced by the insulin only bringing the sugar to normal levels.

A third diabetic, whose sugar level had been well controlled by insulin, produced sweating when the blood-sugar level fell to about 70 mg. per 100 c.cm. (fig. 1, curve F). It has been suggested that a rapid fall in blood sugar may of itself produce symptoms of hypoglycaemia, but symptoms were produced only in that case in which the blood sugar fell below 80 mg. per 100 c.cm.

It would seem that, in this very small group of diabetics, sweating is related to a low level of the blood sugar, and not to the actual falling of a high blood sugar or to the insulin itself.

Sweating following intravenous insulin in children with coeliac disease

Twenty intravenous insulin tolerance tests were performed on thirteen cases of the coeliac syndrome. In every case sweating occurred. The onset of sweating was earlier than in the normal controls and usually continued for at least thirty minutes, or until glucose, adrenaline, or some food had been given (fig. 1, curves C, D, and E).

The sweating and pallor, occurring in these cases with definite relationship to insulin and hypoglycaemia, was that which the nurses spontaneously remarked upon as being a common natural occurrence during the night. This observation was later confirmed by myself and resident house physicians.

The effect of the intramuscular injection of adrenaline on sweating

In one normal case in which sweating occurred early following the injection of insulin, adrenaline was given intramuscularly, and sweating with other symptoms terminated within five minutes with a rapid hypoglycaemic response (fig. 1, curve B).

In two cases of coeliac disease adrenaline was administered following insulin at a time when previous control tests had shown that sweating and hypoglycaemia would continue for a long period. In both of these cases the sweating terminated in about ten minutes following the injection of adrenaline. In one, which was observed longer, sweating was seen to reappear after a further period of twenty minutes. The blood sugar did not rise more than 8 mg. per 100 c.cm. and was still well below the usual symptom-producing level although the sweating ceased. In three cases when sweating was observed in patients with coeliac disease before the commencement of simple adrenaline tolerance tests, the sweating terminated within ten minutes of the injection of the adrenaline.

The only cases in which adrenaline in standard dosage was observed to produce sweating have been in children over the age of twelve who have at the same time felt frightened. In the coeliac cases the injection of adrenaline seemed to make them more happy and more lively than usual. The consistent findings in these cases were that adrenaline terminated the cold sweating, and this effect seems to be quite independent of the actual blood-sugar level.

The effect of oral glucose upon sweating

It has been shown that, following the administration of oral glucose in patients with coeliac disease after an injection of insulin, the blood-sugar returns to normal (Emery, 1946). The sweating invariably associated with the hypoglycaemia in these cases also terminated after a lag period of ten to fifteen minutes from the giving of the glucose. In all eight cases tested, the sweating had ceased before the blood sugar had returned to the resting level (fig. 1, curve D).

Two coeliac patients were observed to be sweating at the commencement of oral glucose tolerance tests. In these the sweating stopped within fifteen minutes of the administration of the glucose, although the blood sugar showed no appreciable rise at that time or subsequently.

Sweating terminated when intramuscular adrenaline and oral glucose were given simultaneously, in these circumstances associated with a great rise in blood-sugar level (fig. 1, curves D and G).

Thus oral glucose is able to terminate cold sweating, and this effect does not seem to be dependent upon the production of a rise in blood-sugar level.

Cold sweating related to intervals between meals

The skin texture of seven patients with coeliac disease and seven controls in adjacent beds were noted hourly over a period of twenty-four hours (table 1). The well-known clinical observation that coeliac children sweat more than others was confirmed. A definite relationship between meal-intervals and sweating was seen. From 6 a.m. to 6 p.m. meals were at three-hourly intervals, with occasional sweets as well, and a small amount of sweating was seen during this time. After 6 p.m. there occurred gaps of five and then six hours, and during this period there was a steady increase in the amount of sweating. This was most marked in the coeliac patients, but was also apparent in the others.

The milky drink given at 4.30 a.m. caused the sweating in the controls to return immediately to day levels, but the coeliac patients required a further meal at 6 a.m. before the sweating was much reduced.

Thus it would seem that in patients with coeliac disease there is a definite relationship between intervals between meals and cold sweating. Further confirmation of this was obtained later when Dr. Beryl Corner agreed to the institution in these cases of small frequent feeds two hourly, both day and night. A marked diminution in sweating occurred, and the general condition of the children also improved. Later, due to a misunderstanding, the night feeds were stopped and the excessive sweating recurred, to be diminished again by night feeds.

Blood-sugar levels related to spontaneous sweating in coeliacs

Samples of blood were taken from two patients with coeliac disease and two normal adjacent children at intervals during the night, and the degree of sweating was noted (table 2). No food was given between 10 p.m. and 6 a.m. At 4 a.m. the coeliacs were sweating while the controls were not. The blood sugars of the coeliacs were 12 and 2 mg. per 100 c.cm. and the others 11 and 0 mg. per 100 c.cm. below the 11 p.m. levels. The greatest variation in blood sugar of the coeliac patients during the night was between 99 and 104 mg. per 100 c.cm., and that of the others between 74 and 85 mg. per 100 c.cm. After the 6 a.m. feed a rise in blood sugar was more marked in the non-coeliacs. Two observations of interest seem to follow from these figures: (a) the sweating does not seem to be related to the actual level of the blood sugar. Coeliac B sweated with a blood sugar of 99 mg. per 100 c.cm., while control B did not sweat with a sugar level at the same time of 71 mg. per 100 c.cm.; (b) the amount of sweating does not seem to depend on a fall in blood sugar. (In coeliac A the 11 p.m. and 2 a.m. levels were the same, while sweating was much more profuse at 2 a.m. than at 11 p.m.)

Table 2

GIVING THE BLOOD-SUGAR LEVELS AND SWEATING CATEGORIES OF TWO COELIAC AND TWO NON-COELIAC CHILDREN IN ADJACENT BEDS DURING A NIGHT FAST

		p.m. 11	12	1	2	a.m. 3	4	5	6	7	8
Coeliac (A)	Blood Sugar	68	—	—	68	—	56	—	69	—	69
	Sweating	1	—	—	3	—	4	—	0	—	0
Coeliac (B)	Blood Sugar	101	—	—	104	—	99	—	104	—	104
	Sweating	0	—	—	0	—	2	—	0	—	0
Non-Coeliac (A)	Blood Sugar	85	—	—	71	—	74	—	89	—	94
	Sweating	0	—	—	0	—	0	—	0	—	0
Non-Coeliac (B)	Blood Sugar	99	—	—	99	—	99	—	91	—	114
	Sweating	0	—	—	0	—	0	—	0	—	0

Fasting sugar levels in coeliacs and controls

The hundred and fifty-four estimations of the fasting sugar level were made during investigations on thirteen cases of the coeliac syndrome and eighty estimations under similar conditions in control patients. The mean level of the patients with coeliac disease was 93 mg. per 100 c.cm. of blood, and the controls 85·6 mg. per 100 c.cm. Fig. 2 shows the percentage frequency curves of these observations and it will be seen that the sugar levels in both groups have virtually the same range and distribution. It would thus seem that although in patients with coeliac disease there is a state of carbohydrate insufficiency this does not show itself by any lowering of the resting blood sugar.

Discussion

All recent publications have recognized that cold sweating is a symptom of hypoglycaemia (Himwich, 1944) and almost all observers within their own series remark upon the variation in different cases between symptoms and the actual sugar level (see Wauchope's review, 1933). In these investigations

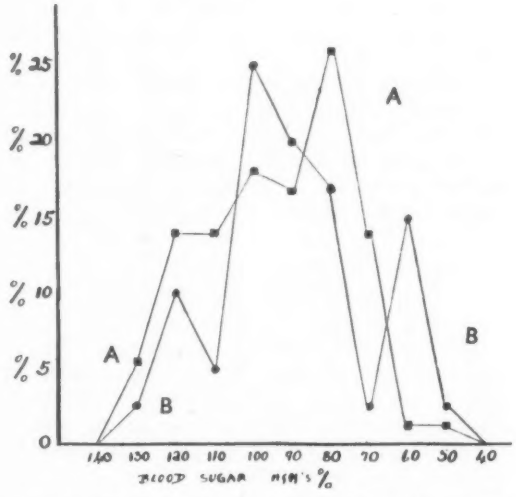


Fig. 2.—Showing percentage distribution curves of the four-hour fasting sugar level in children with the coeliac syndrome (154 estimations) and in control convalescent children (80 estimations). A=coeliac. B=normal.

a similar relationship has been noted between hypoglycaemia and cold sweating in convalescent children, and cases of coeliac disease and diabetes. The most significant finding is, however, the lack of correlation between the actual level of the blood sugar and the cold sweating. This is seen in the sweating of fasting and in that produced by insulin. The most marked dissociation was seen when sweating was terminated by glucose and adrenaline following insulin. It is, nevertheless, probably correct to say that sweating can be induced in any child provided the blood sugar is lowered enough by insulin. Furthermore, while it is definite that children with coeliac disease are much more liable to cold sweats than other children, it is equally demonstrated that the blood-sugar level in the fasting state is at least as high as normal.

The question that immediately arises is whether the sweating produced by insulin is of the same etiology as that occurring spontaneously related to food. It is well recognized that in adults there are many causes of cold sweating (List and Peet, 1938) but little work seems to have been done on children. The sweating of hypoglycaemia and that of fasting both respond similarly to the administration of oral glucose and intramuscular adrenaline: and this of itself is enough to suggest a common background, probably of acute glucose deficiency.

That starvation does not produce a lowering of the blood sugar in children was shown by Ross and Josephs (1924) and it would have been surprising, if, in the long fasting periods when sweating occurred, the blood sugar had fallen to any great extent. It is most probable that the cold sweating to which coeliacs are abnormally liable is related to their lack of available glucose (or some closely related substance). The position seems to be that sweating is often related to the lowering of the blood sugar, but it is not dependent upon the sugar level, and is more dependent upon the state of carbohydrate metabolism which is liable to be associated with a fall of blood sugar. As oral glucose terminates this sweating, its cause could be an acute lack of available glucose products; and this theory would adequately explain all the observed reactions and does not entail a static symptom-producing level of the blood sugar. The work on pyruvic acid and lactic acid would seem to support this thesis, as there does not seem to be a direct positive relationship between these substances and the blood-sugar level (Gillman and Golberg, 1943).

Two further points arise from these experiments, one concerning the action of adrenaline, and the other the lag period before the onset of symptoms.

Adrenaline appears to terminate the cold sweating with or without raising the blood-sugar level, and the most simple explanation of this would be that it makes some form of carbohydrate available. But it is very difficult to be certain in the body as to what reaction is necessarily a primary response to adrenaline. Since Cannon's work on hypoglycaemia, in which he demonstrated an increased output of adrenaline in hypoglycaemia by its action on the denervated heart, it has been generally assumed that the early symptoms of hypoglycaemia are due to an increased output of adrenaline. That such an explanation was not the complete picture was early demonstrated by the inhibition by adrenaline of hunger and hypoglycaemia contraction of the stomach (Bulatao and Carlson, 1924), and it is possible that sweating is an allied reaction. Further investigations are needed in humans.

The lag period between the blood sugar reaching low levels and the onset of symptoms varied from ten to twenty-five minutes; and in cases showing normal hypoglycaemia responsiveness this may lead to confusion clinically. Blood taken during or immediately following symptoms, if the latter are of short duration, will often give no hint of the previous low level of the blood sugar (fig. 1, curve A). Thus, single estimations of the blood sugar may be misleading when hypoglycaemia is suspected, as are cerebrospinal fluid glucose levels in hypoglycaemic coma (Mayer-Gross and Walker, 1945). In this paper the term hypoglycaemia has referred to a lowering of a previously known resting sugar level, and not to any particular sugar level.

Conclusion

Cold sweating in patients with coeliac disease can be interpreted as being due to an acute carbohydrate insufficiency whatever the blood-sugar level. It does not necessarily follow that the same applies to cold sweating in any ill child, but the findings reported indicate that the observation of cold sweating in any child should suggest the possibility of carbohydrate insufficiency and merit the administration of glucose.

> ' His stomach is the kitchen where the meat
> Is often but half sod, for want of heat.'
>
> (From Gee's (1888) original description of the coeliac syndrome.)

Summary.

1. Cold sweating often follows the lowering of the blood sugar by insulin (after a lag period of ten to twenty minutes).

2. A similar cold sweating occurs spontaneously in patients with coeliac disease, particularly after fasting.

3. Cold sweating following insulin and occurring spontaneously is relieved by glucose and/or adrenaline.

4. Children with coeliac disease are particularly prone to cold sweating but their fasting blood-sugar levels are at least as high as normal.

5. Cold sweating is not dependent upon any actual level of the blood sugar.

6. It is suggested that cold sweating in children with coeliac disease, and also possibly in other ill children, may often be due to acute carbohydrate insufficiency independent of the blood sugar level.

7. It is suggested that ill children liable to cold sweating should be given frequent feeds day and night.

Thanks are due to the nursing staff of the Bristol Children's Hospital for their help in these investigations, and to the medical staff for freedom to use their patients; to Professor T. F. Hewer for facilities, and to colleagues of the University department for assistance with proofs. In particular I would like to thank Professor C. Bruce Perry for his interest and advice, and Dr. B. D. Corner for her confidence and co-operation in making alterations in the treatment of her patients.

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CARBOHYDRATE METABOLISM IN THE COELIAC SYNDROME

BY

J. L. EMERY, M.B., Ch.B., D.C.H.

(From the Department of Pathology, University of Bristol)

The coeliac sydrome presents one of the most obscure yet fascinating problems of childhood. Recently interest has centred around the possible causes of this disorder; but, after known causes have been eliminated, the majority of cases are classed as post-infective or idiopathic. Change in fat metabolism is the most obvious characteristic of the syndrome, but it is by no means certain in which system the primary disorder lies. The recent work of Andersen (1945) suggests that fat analysis will soon be placed on a more accurate basis. Meanwhile our knowledge of the disorder itself does not greatly advance, and we are confronted with a starvation syndrome in which it is orthodox treatment virtually to starve the patient of fat and carbohydrate.

Investigations involving respiratory exchanges and heat production are extremely difficult to carry out in children, particularly in the age groups showing the syndrome in its most severe form. Fleming and Hutchison (1924) carried out their investigations on marasmic children at rest after feeding. Thaysen (1929, 1935), maintaining that the coeliac state is juvenile sprue, overcame the difficulty by investigating cases of adult non-tropical sprue, and also one child aged eleven. He showed that the ingestion of glucose in sprue produced a marked rise in the respiratory quotient, associated with a flat oral glucose-tolerance curve, and concluded that glucose is absorbed normally and utilized very rapidly in these cases. There has since been a series of papers (Crawford, 1939; Badenoch and Morris, 1936; Parsons, 1932; Ross and Tonks, 1938) in which the conclusion is directly opposite, i.e. that there is in the coeliac syndrome a defective absorption of glucose. The latter view appears now to be generally accepted. These investigations, however, show several inconsistencies. Thus, Ross and Tonks (1938) describe a diminished sensitivity to insulin, while Badenoch and Morris (1936) show an increased sensitivity to the same dose. Ross and Tonks find also a reduced intravenous glucose tolerance, while Crawford (1939) describes it as normal. Furthermore, dosage has often not been directly related to body weight. In view of the apparent contradiction in these observations and conclusions, it was considered that a reinvestigation of the problem would be of value.

Selection of Cases

The material consisted of thirteen cases. In all, the onset was after weaning. All showed wasting, hypotonia, deflated buttocks, distended abdomen, steatorrhoea, and fat intolerance; also stunting of growth, hypochromic anaemia, capricious appetite and bowel action, and a tendency to wide variation in day-to-day body weight. There was no frank or radiological rickets. Duodenal intubation for the detection of pancreatic insufficiency could be performed only in three cases, and gave normal trypsin levels (using the technique of Andersen and Early, 1942). No case was included unless it showed a flat oral glucose-tolerance curve. (Note: following the observations of Thaysen (1929), Svensgaard (1931), and MacLean and Sullivan (1929), considerable interest in the low blood-sugar curve in sprue and in the 'coeliac' syndrome has led to this finding becoming one of the diagnostic criteria of these disorders. A low curve is considered to be one showing a rise in blood sugar less than 40 mg. per 100 c.cm. of blood above fasting level, where the intervals of blood sampling are fifteen minutes or less). Details of the cases are included in fig. 1.

Controls. Control cases were of necessity convalescents. The older children were convalescent cases of erythema nodosum; younger children were healthy 'lodgers.'

Scope of present investigation. Using carefully regulated dosage, the investigations on which most of the theories have been based have been repeated, i.e. oral glucose tolerance, intravenous glucose tolerance, and intravenous insulin tolerance. Following this, the same dose of glucose which produced a flat sugar curve was given orally in combination

with insulin and adrenaline, in such a way as to throw into relief any absorption or lack of absorption of glucose. Other tests concerned the underlying state of carbohydrate metabolism.

Methods of investigation. Dosage in all cases was carefully related to the actual body weight. In order to minimize variations in the general condition, the various tests were carried out on each patient as far as possible on succeeding days. The children were starved for four hours before each test; usually they had breakfast at 6.30 a.m., the test starting about 10.30 a.m. Meals missed during the morning were made up in the afternoon and evening. Rudeshill and Henderson (1941) observed that, in children, the blood-sugar level three and a half hours after a meal may be substituted for the fasting blood-sugar level. Acting on this observation, and so that as little break in the daily routine as possible might be required, the four-hour fasting period was taken.

Blood was taken from the heel or great toe direct into a 0·2 c.cm. unoxalated Ostwald pipette. The method of sugar estimation was that of Folin and Wu, using a Kleet colorimeter. All manipulations of dosage, blood-taking, and estimation were carried out personally. In the curves reported, the resting sugar level is quoted as one figure; in most cases this denotes the mean of two samples taken in immediate succession. The difference in these two readings was usually 2 mg. per 100 c.cm. of blood or less, rarely as much as 5 mg. The oral glucose tolerance test was always carried out first, and simple insulin tolerance preceded the other tests involving the use of insulin. Daily variation in response could be allowed for only by varying the order of the tests, which, except for those previously mentioned, were performed in a haphazard order. It is thought that the uniformity of the response obtained is sufficient to prove the points mentioned at the end of each section.

Technical Details and Comments on Tests

Oral glucose tolerance. Glucose was given in the child's ordinary feeding cup, with about 60 c.cm. of water in the dosage of 1 g. per kg. of actual body weight. After this had been drunk, the cup was again partly filled with water and presented to the child to satisfy its thirst; 100 c.cm. in all was allowed, and no subsequent fluid was given. All the children took the glucose readily, and no retching or vomiting occurred.

Intravenous insulin tolerance. This test consisted in the intravenous administration of 0·1 units of soluble insulin per kg. of actual body weight, and in the noting of the blood-sugar level for at least two hours afterwards. Crawford (1939) reports the response to insulin as normal, but her observations were carried out over one hour only, and an analysis of her results shows the blood-sugar level to be falling at the end of an hour (her cases 3 and 5). Badenoch and Morris (1936), using a subcutaneous dose of insulin (4 units for all ages), showed a greater fall in blood sugar than normal, while Ross (1938), using the same dose intravenously, showed a depression smaller than normal. The test measures two distinct process: (a) the sensitivity of the blood-sugar level to insulin, and (b) the reaction of the body to a lowered blood glucose.

Intravenous insulin followed by oral glucose. The observation that the blood sugar remains low after the administration of insulin in 'coeliacs' suggested that the reaction be used to produce a sensitized state for the administration of oral glucose. The same dose of glucose was given as in the oral glucose-tolerance test, but at a time when the blood sugar was low and unlikely to rise spontaneously to normal (as judged by a previous curve on the patient).

Adrenaline after insulin. The response to adrenaline during prolonged hypoglycaemia due to insulin has been used as a test of pituitary function (Fraser et al., 1941). The dosage used by these observers was employed in the present series—i.e. 0·001 mg. per kg. of body weight intramuscularly. They consider that a response to adrenaline at the 120-minute period is indicative of a lack of hypoglycaemia-sensitivity, due to a failure of the response mechanism centred in the pituitary.

Adrenaline response at normal fasting level. The standard dose of adrenaline related to body weight was given intramuscularly (deltoid).

Oral glucose with intramuscular adrenaline. This test consisted essentially of combining the oral glucose test with the adrenaline test. The adrenaline was injected at the same time as the glucose (the same dose as was used in the previous tolerance test) was taken by mouth.

Intravenous glucose tolerance. The technique of this test—as regards dosage of glucose, interval of testing, and method of administration—varies with different observers. Ross, whose findings conflict with most others, cuts down on a vein—considering that this disturbs the child less than direct venepuncture. In the present cases, after the fasting samples of blood from the heel had been taken, 0·5 g. of dextrose per kg. of body weight in the form of a 25 per cent. solution in normal saline, was injected directly into a vein with a large syringe. Needle and vein were then washed through with a further 2 c.cm. of saline from a second syringe. The time taken over the injection was usually one minute, and always under two. The first blood specimen was then taken immediately; the subsequent intervals corresponded approximately with those used by Ross.

Method of charting. In order to make the diagrams clear, the curves (except in fig. 8) are shown in mg. per 100 c.cm. of blood, rising or falling from the resting blood-sugar level. The key to the cases is tabulated in fig. 1, and as it applies to all the charts it is not repeated.

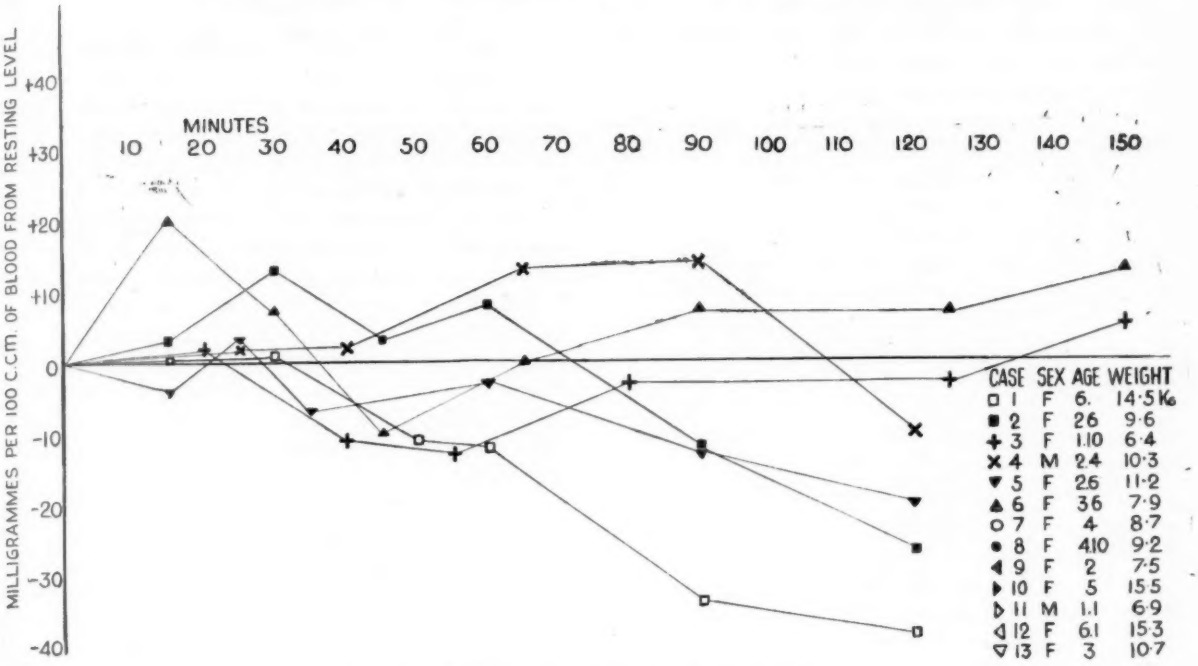

FIG. 1.—Oral glucose tolerance (cases 1 to 6).

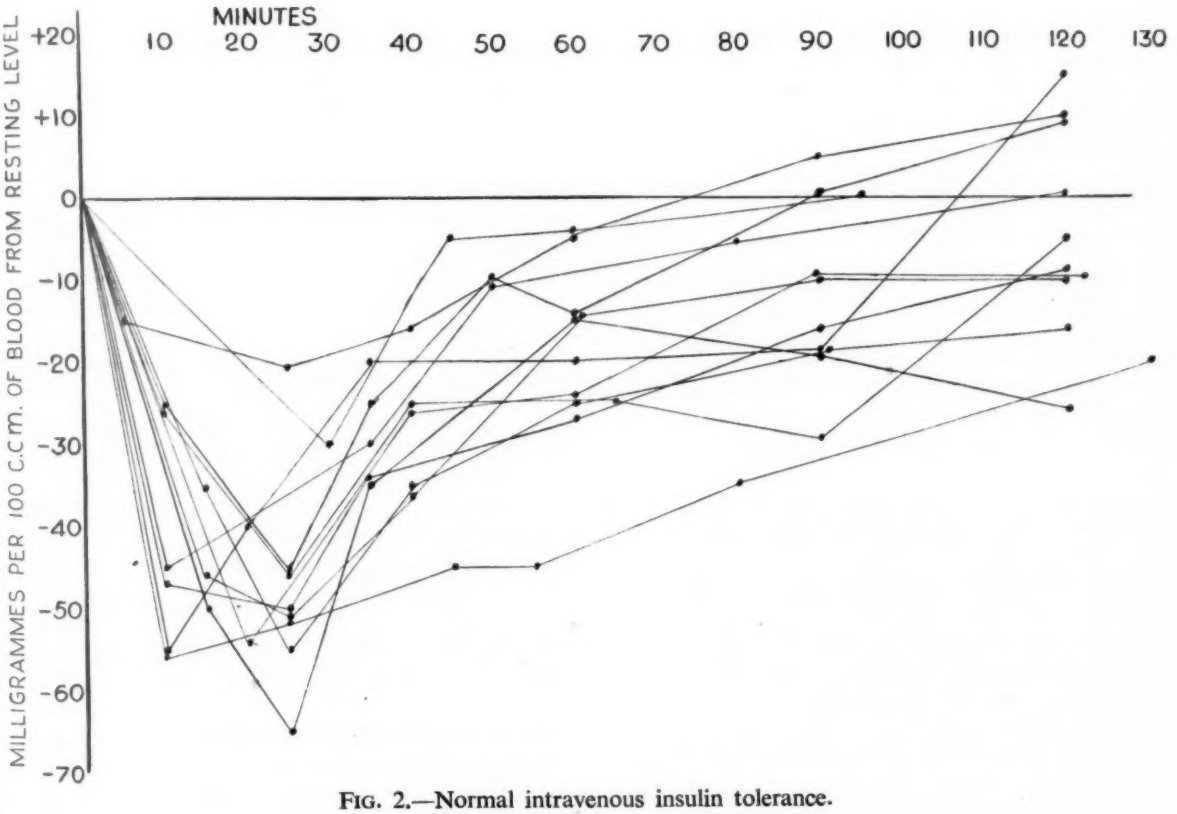

FIG. 2.—Normal intravenous insulin tolerance.

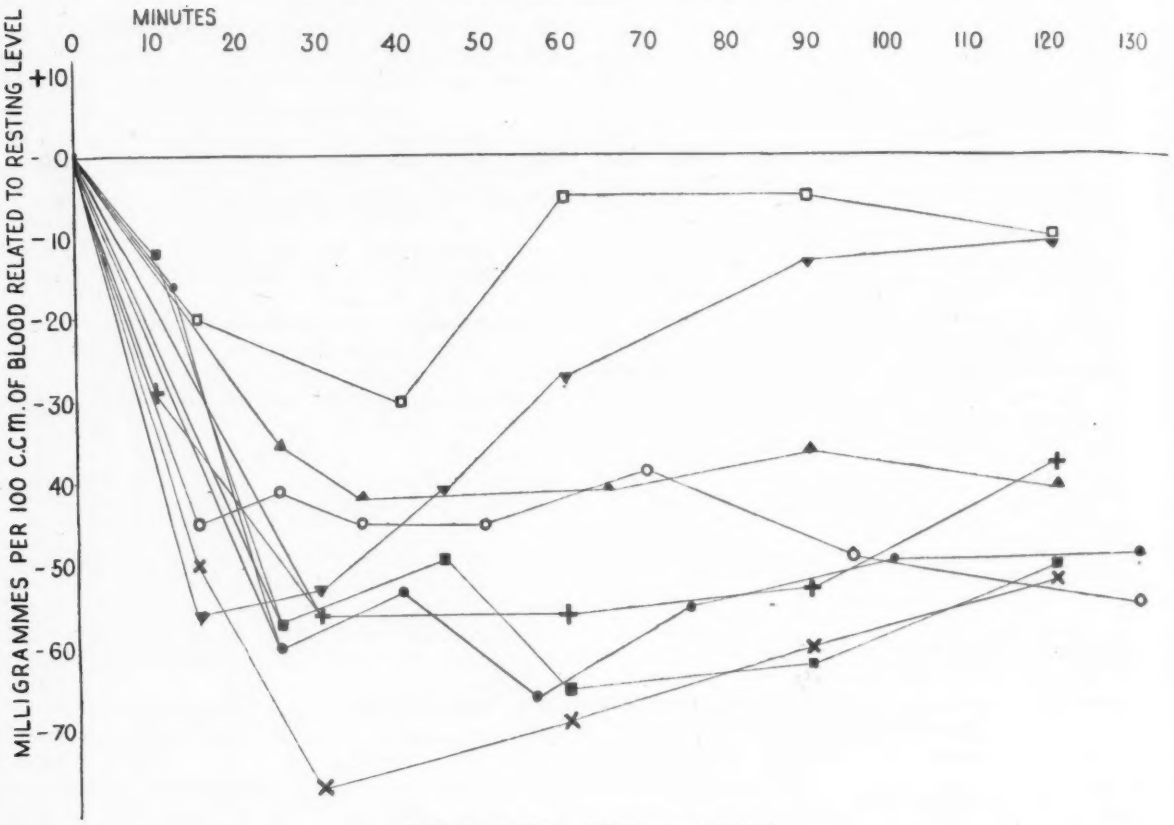

FIG. 3.—Insulin tolerance: 'coeliac.

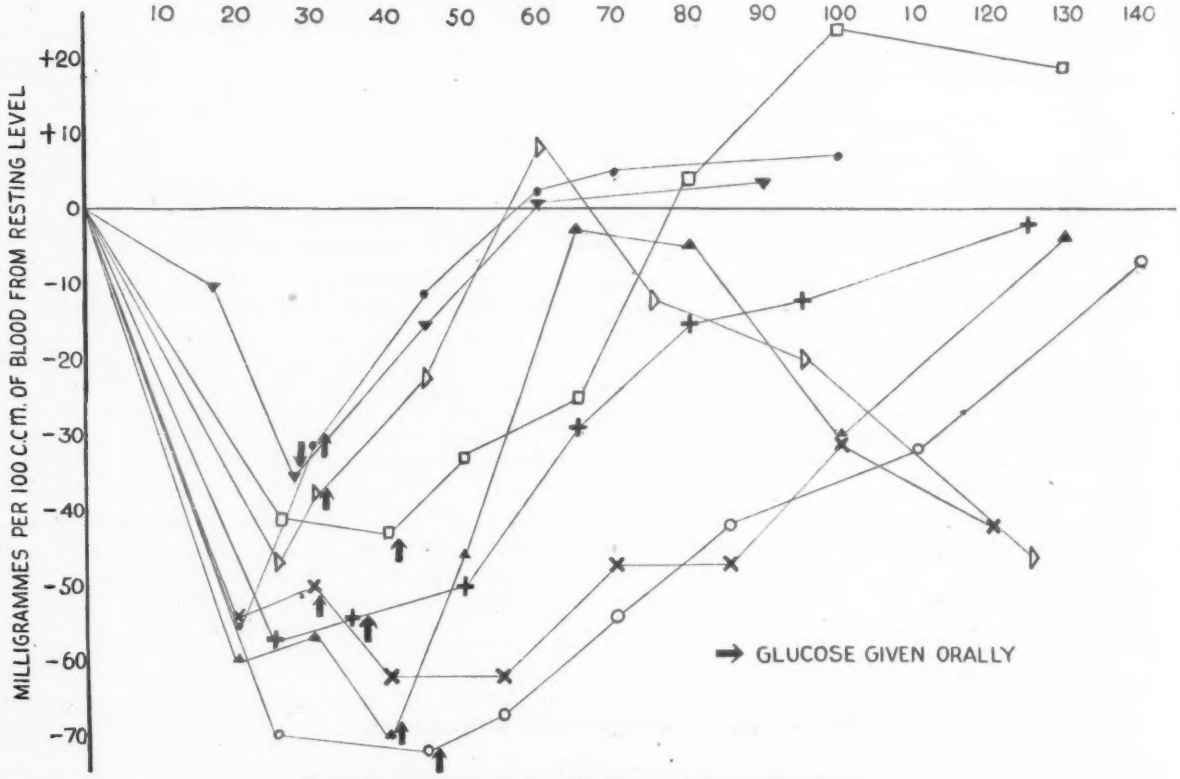

FIG. 4.—Intravenous insulin followed by oral glucose.

Results

Oral glucose tolerance. (Fig. 1.) It was seen that the majority of curves showed no appreciable rise in blood sugar. The purpose of reproducing some of the curves is to draw attention to specific features of form. In cases 1, 2, and 5, there occurs after the 60-minute period a definite depression of the blood-sugar level. This depression is seen in the 40- to 60-minute period in case 3. This period of depression, although not constant, can be seen in other reported cases, e.g. curves (b) and (c) in case 1 of Svensgaard. It is possible that this depression corresponds to the depression often noted at the end of a normal glucose-tolerance curve, due to a temporary overaction of the mechanism immobilizing glucose. It may be said with some justification that this degree of variation is within the limits of the normal variation in sugar level, errors in technique, and nervous reaction: but the latter usually shows itself by a raising of the blood-sugar level. The constancy of this period of depression is at least noteworthy. Thus in some cases of the coeliac syndrome the oral glucose tolerance curves show a period of blood-sugar depression which may correspond to similar depressions in normal curves and indicate that the body is reacting as if glucose were absorbed.

Intravenous insulin tolerance. (Figs. 2 and 3.) The curves may be analysed in two parts: (a) the first 30 minutes, which includes the immediate glycolytic response to the injected insulin; and (b) the following 90 minutes, which demonstrate the reaction to the reduced blood sugar.

(a) THE FIRST 30 MINUTES.—It would be easy to miss a maximal peak in the fall of the blood sugar by taking specimens at 10-minute intervals. For this reason the area, mg.-minute, depression of the first 30 minutes would give a more reliable criterion for comparison. In twelve control curves the mean volume was 950 mg.-minute (varying from 482 to 1,192). In twenty curves covering the same period in coeliac children the mean volume was 911 mg.-minute (varying from 495 to 1,397). It is considered that these figures, in association with the general similarity of the curves in their angle of fall, justify the conclusion that the immediate response to insulin as portrayed by a fall in blood sugar is normal.

(b) THE LATER 90 MINUTES.—Here there is a marked difference between 'coeliacs' and controls. At 50 minutes and subsequently all but one of the controls show a blood-sugar level within 30 mg. per 100 c.cm. of blood below the fasting level, and by two hours they are fairly well grouped about the fasting level. In the 'coeliacs' two curves are within normal limits (cases 1 and 5). The remaining seven curves show what is termed 'hypoglycaemic unresponsiveness.' This phase does not show a completely uniform level, but most curves have an initial slight rise which is not maintained. The significance of this reaction is not easy to assess. However, in view of this apparently normal initial response (which was also observed by Crawford), it is thought that it is justifiable to discard the concept of failure of the pituitary-thyroid-adrenal mechanism, and to consider glycogen deficiency as the most likely explanation. This point requires further investigation, both in other types of marasmus and in cases of liver deficiency. Thus in 'coeliacs' the immediate reaction to intravenous insulin is normal, but there is, generally, an inability to regain the original blood-sugar level after hypoglycaemia produced by insulin.

Intravenous insulin followed by oral glucose. (Fig. 4.) The significance of these curves can best be assessed when compared with the other curves of the same patient, but the difference between figs. 3 and 4 is evident—in general the curves are transformed to normal insulin response curves. Case 11 is unique in that there is an immediate rise to above the resting level, followed by a steady fall, so that at 120 minutes the same level is reached as where no glucose is given orally. Case 2 (not included in fig. 4) showed a remarkable and rapid rise after a three-hour period of hypoglycaemia, thus suggesting the possibility that the longer the period of hypoglycaemia the more rapid the eventual absorption of glucose. Thus, in 'coeliacs,' glucose by mouth, in dosage insufficient to produce a rise in blood sugar when the latter is at resting level, produces a marked rise when the blood sugar has been lowered by insulin.

Adrenaline after insulin. Four 'coeliacs' at the 120-minute period produced, with adrenaline, rises of 26, 16, 20, and 18 mg. per 100 c.cm. of blood respectively during the next 30 minutes. It did not seem justifiable to do control curves to cover this period. In two cases the adrenaline was given at a point corresponding to that at which glucose was given after insulin (fig. 5). The response is distinctly abnormal, there being a very small rise in blood sugar—and that not maintained. This same slight rise was noted in the simple insulin-depression curves in these cases, and thus it seems that the adrenaline does not affect the nature of the curves. Thus in 'coeliacs' adrenaline fails to produce a normal response in the early hypoglycaemic phase after insulin, but adrenaline does produce some response two hours after insulin has been given. As the usual 'coeliac' curve is not

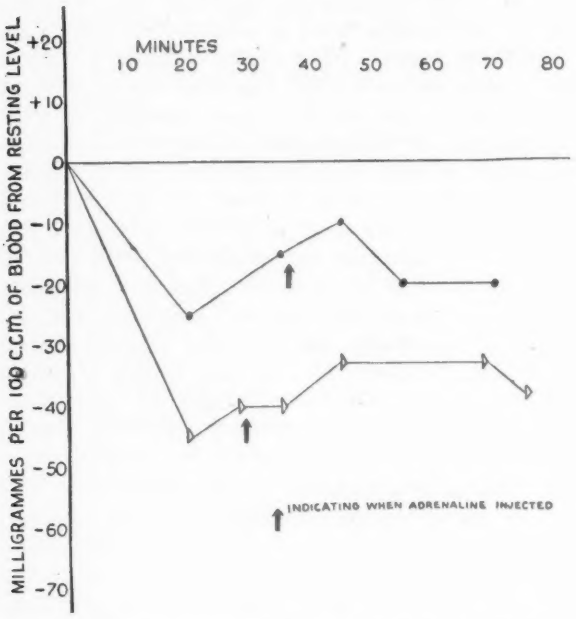

FIG. 5.—Intravenous insulin followed by adrenaline.

altered by adrenaline, it would seem that the abnormality of the curve is not due to a lack of adrenaline.

Adrenaline response at normal fasting level. (Fig. 6.) In nine control cases the mean mg.-minute area for 60 minutes was 1,512. In all, fifteen tests were performed on the 'coeliacs' (in three cases two curves were obtained); the mean mg.-minute area was 933. Inspection of the curves shows that they differ chiefly in the first 20 minutes, the rate of blood-sugar rise being slower in the test cases. Thus 'coeliacs' show a diminished glycaemic response to adrenaline in the fasting state. The rate of rise of the blood sugar following the injection of adrenaline is slower than normal.

Oral glucose with intramuscular adrenaline. (Fig. 7.) Six 'coeliacs' and two controls were used. Although so few controls were employed, the curves appear to be within normal limits. It will be noted that in the first 20 minutes the graphs are remarkably similar. In the table the 60-minute areas of the curves obtained are analysed. It will be seen that in the 'coeliacs' the sum of the volumes of the separate oral glucose and adrenaline responses is far short of the volume obtained when adrenaline is combined with the oral glucose. This does not occur with the controls. Thus in

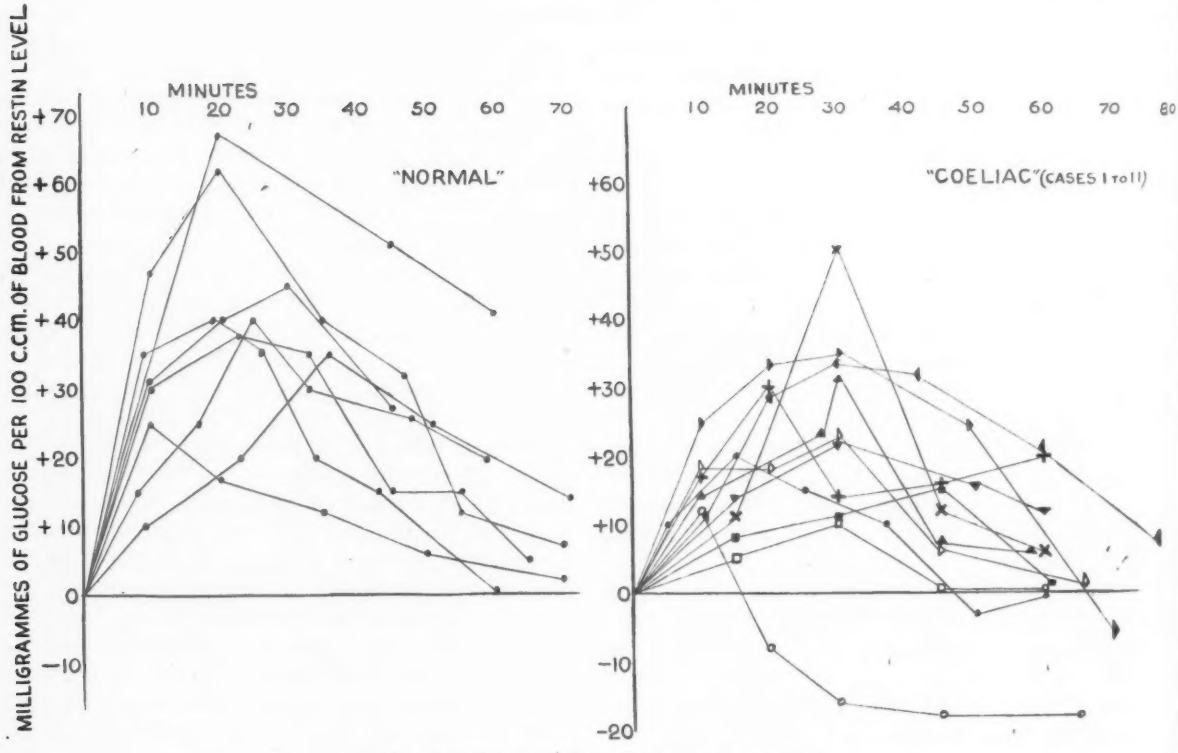

FIG. 6.—Intramuscular adrenaline response.

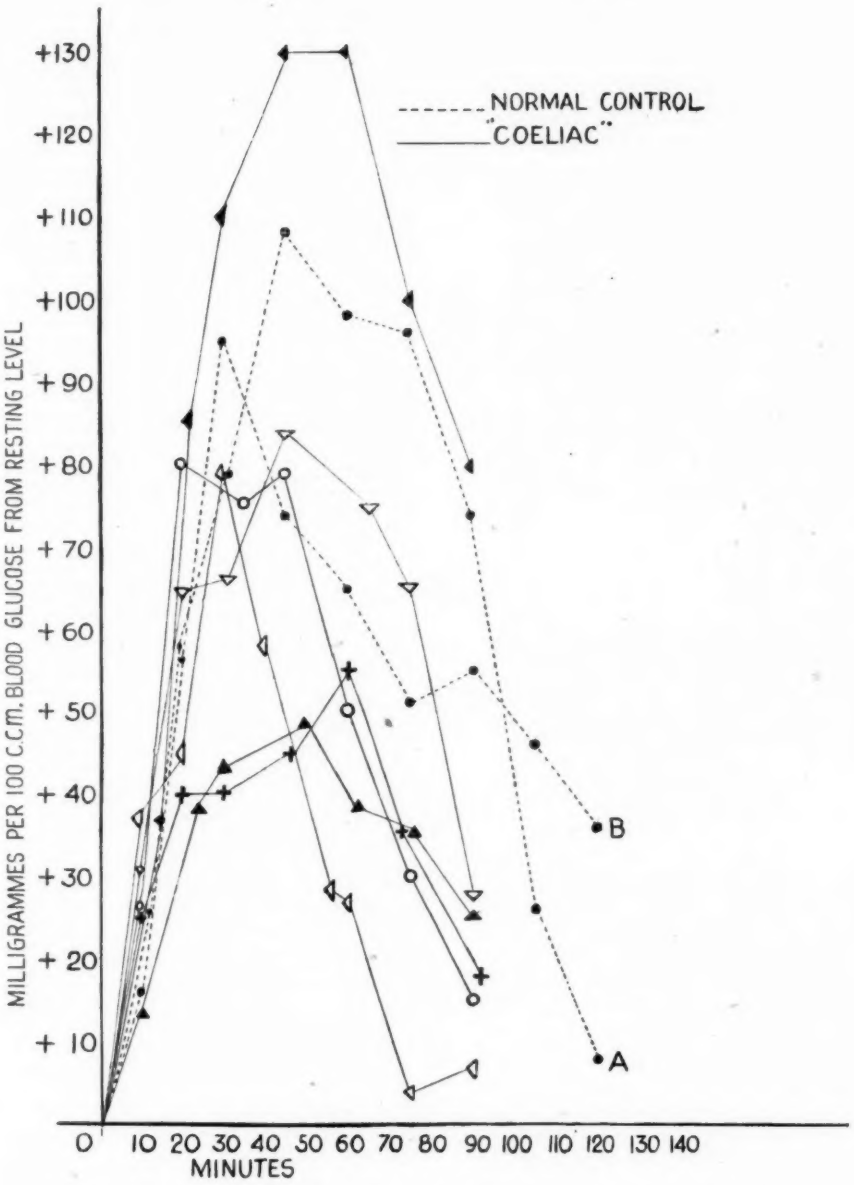

FIG. 7.—Combined test. Oral glucose and intramuscular adrenaline.

'coeliacs' the rise in blood sugar following the combined administration of oral glucose with intramuscular adrenaline is within normal limits. The response to the combined administration of oral glucose and parenteral adrenaline greatly exceeds the sum of the separate responses.

Intravenous glucose tolerance. (Fig. 8.) The curves obtained in the 'coeliacs' and controls are essentially the same (as was found by Crawford). The curve from case 11 is included, as it is the only one approximating to those of Ross. It was obtained in unusual circumstances. At the time of the test the child, with a staphylococcal infection, was within a few hours of death and the glucose was administered through a transfusion apparatus that had previously been set up.

Thus intravenous glucose tolerance in 'coeliacs' is within normal limits. Tolerance may be impaired during an infection.

TABLE SHOWING THE RELATIONSHIP OF THE VOLUMES OF THE CURVES OBTAINED WITH ORAL GLUCOSE AND WITH INTRAMUSCULAR ADRENALINE, AND IN THE COMBINED TEST. ALL FIGURES ARE MILLIGRAMME-MINUTE VOLUMES FOR 60 MINUTES.

Coeliac	Oral glucose tolerance	Adrenaline tolerance	The sum of oral glucose tolerance + adrenaline tolerance	Combined test—oral glucose with adrenaline	Difference
A.Z.	354	875	1,229	3,415	+2,186
B.Y.	280	902	1,182	2,234	+1,052
H.W... ..	1,477	1,443	2,920	5,286	+2,366
D.T.	822	715	1,537	2,242	+ 705
E.S.	−320	1,035	715	1,952	+1,237
K.P.	785	2,355	3,140	3,592	+ 452
CONTROL:					
L.G.	787	2,700	3,487	3,560	+ 73
M.J.	3,150	1,817	4,967	3,620	−1,347

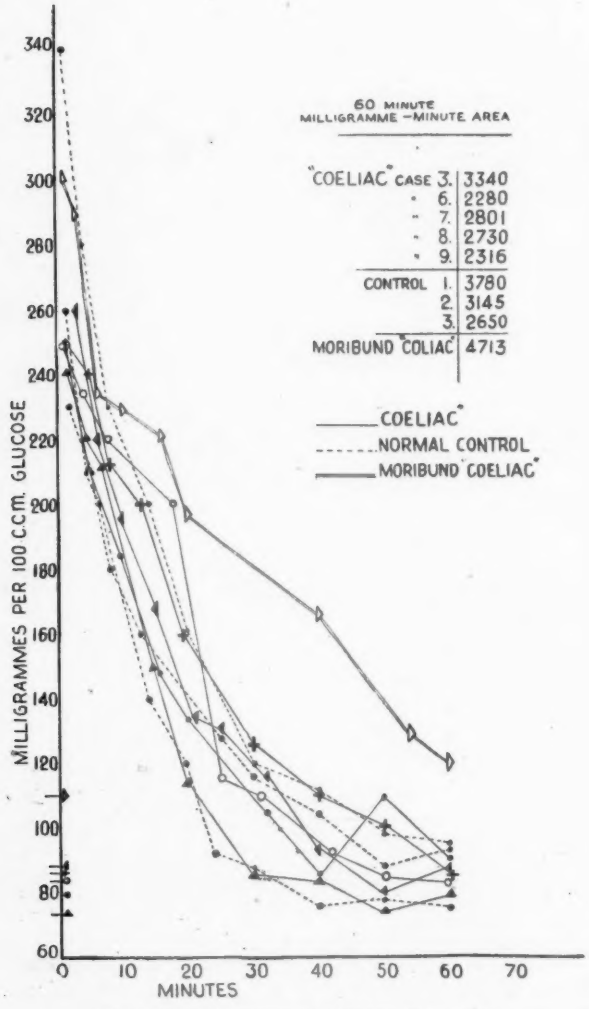

FIG. 8.—Intravenous glucose tolerance.

Discussion

It is difficult to see any other reasonable explanation of the response to oral glucose after insulin than that, in 'coeliacs,' glucose is absorbed. Similarly, judging from the normal response to the combined adrenaline and oral glucose, it appears to be absorbed at the normal rate.

If it is accepted that glucose absorption is normal, the flat oral glucose-tolerance curve indicates a more rapid fixation of glucose. The finding of normal intravenous glucose tolerance at first sight seems to contradict this; but there are two other factors to be considered: (a) to produce a rise in peripheral blood sugar the absorbed glucose must first have passed through the liver; (b) all observers agree that a normal oral glucose-tolerance curve is obtained in 'coeliacs' if a large dose of glucose is given. Thus it is only legitimate to relate directly oral and intravenous glucose tolerance if the liver is functioning normally as regards glucose, or even more correctly when the liver tends to let glucose through (diabetes mellitus is the disorder in which these tests have been most used). It is reasonable to suppose that if the liver is deficient in glycogen it would immediately take up a small quantity of glucose. Mirsky and Nelson (1944) showed that the normal immediate liver glucose reserve in a child lies between 15 and 20 g. If in 'coeliacs' the reserve is lacking, a quantity of glucose in the region of 10 g. reaching the liver via the portal vein would be immediately fixed. This is the quantity of glucose given in the present series of investigations. Larger doses would be expected to produce a rise in the peripheral blood sugar only.

A deficiency of liver glycogen is also the most reasonable explanation for the failure of the blood

sugar to regain its original level after intravenous insulin; the small immediate rise seen may be due to a small quantity deposited as glycogen by the insulin.

The adrenaline responses are more obscure. In intact animals, Cori (1931) noted no increase in the A.V. blood-sugar difference after the administration of adrenaline; and Bridge and Noltie (1935) observed that, after intravenous injection of adrenaline, the respiratory quotient fell to the fat-protein level. (Himsworth and Scott (1938), using rabbits with excluded livers, obtained different results.) The adrenaline response in 'coeliacs' is smaller than normal, but, if the glycogen stores of the body are as low as we suspect, it is surprising that the response is as great as it is. The difference between the responses with adrenaline alone, and with oral glucose and adrenaline, indicates that in these cases adrenaline virtually prevents the immediate demobilization of glucose. The delayed response to adrenaline in these cases could well be due to a lack of immediately available glycogen for glycogenolysis, while the general response is possibly due to glucose produced from fat and/or protein, with possible failure of utilization. At this point in these investigations it would be premature to relate adrenaline directly to the etiology of the coeliac syndrome; but the observations of Hill and Koehler (1932) that the administration of adrenaline to rats produced an increase of 100 per cent. in faecal lipid excretion may be relevant here.

Summary

The findings in the coeliac syndrome may be summarized as follows:

1. Oral glucose-tolerance curves are flat, and, in addition, may show periods of actual fall in blood-sugar level.

2. The immediate fall in blood sugar due to insulin is normal. There is usually a failure of the blood sugar to regain its original level in the normal time, although after the original fall there is often a temporary rise.

3. The relative failure of the blood sugar to rise after administration of insulin is not affected by adrenaline: this suggests that there is no deficiency of that substance.

4. Oral glucose, when the blood sugar is low after insulin, does restore the blood sugar to normal.

5. Adrenaline, when not preceded by insulin, produces a rise in blood sugar which is less than the normal. This difference is most noticeable in the early period, when the rise is less rapid.

6. When oral glucose is given at the same time as adrenaline there is an immediate and rapid rise in blood-sugar level—as in normal subjects.

7. Intravenous glucose is removed from the peripheral blood stream at a normal rate.

Direct and indirect evidence has been produced to show that children in the 'coeliac' state can absorb glucose normally, can also utilize it normally, but lack available glucose. Thus the carbohydrate metabolism in these children appears to correspond with that in other marasmic states, as demonstrated by Fleming and Hutchison (1924), and by Tisdall et al. (1925).

Thanks are due to the Honorary Staff of the Bristol Children's Hospital for allowing the investigations upon their patients, and also to Prof. T. F. Hewer, Dr. Beryl Corner, and Dr. J. Apley for criticism of the manuscript. In particular I would like to thank Prof. C. Bruce Perry for his guidance and for the interest he has taken in this investigation.

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BLOOD VOLUME CHANGES IN ANAEMIA FOLLOWING TRANSFUSION

BY

SHEENAH J. M. RUSSELL, M.B., Ch.B.

(From the Royal Hospital for Sick Children, Glasgow, and the Department of Medical Paediatrics, University of Glasgow)

Investigations by various workers from the time of Valentin (1847) to the present day have shown that the blood volume is not a constant, and that there exists a state of 'ebb and flow' between the plasma and the tissue fluids. The haemodilution which occurs after acute reduction of the blood volume following a haemorrhage has been observed frequently (Boycott and Douglas, 1909; Robertson and Bock, 1919; Wallace and Sharpey-Schäfer, 1941), while the converse reaction—the occurrence of fluid shifts following the transfusion of serum and blood—has also been recognized and studied (Boycott and Oakley, 1934; Sharpey-Schäfer and Wallace, 1942a; Hayward and Jordan, 1942; Beattie, 1942).

The following two cases of anaemia are reported in view of the completely different responses to blood transfusion, the one reacting by the addition of fluid to the blood stream, the other by the loss of fluid. The initial blood volumes were determined by a dye dilution method, using Congo red to determine the plasma volume, and the haematocrit readings to calculate the total blood volume. In the recent blood volume estimations Evans blue has been used, but the results agree within 10 per cent. of those obtained by Congo red. The haemoglobin values of the transfused blood, and those of the patients before and at intervals after transfusion, were estimated by an acid haematin method on a photo-electric colorimeter.

Case Histories

Case 1. J. L., aged six years, admitted October 2, 1945, was a coeliac dwarf, 53 per cent. of expected weight and 86 per cent. of expected height. He had a severe macrocytic anaemia, which failed to respond to liver and iron. On October 4, the blood picture was as follows: Haemoglobin, 2·9 g. per cent.; erythrocytes, 990,000 per c.mm.; leucocytes, 7,000 per c.mm.; haematocrit reading, 11·3 per cent.; mean corpuscular volume, 11·4 c.μ; mean corpuscular haemoglobin concentration, 26 per cent.; mean corpuscular diameter, 8μ; total plasma protein, 4·35 g. per cent.

The total blood volume before transfusion was 843 c.cm. (7·8 per cent. body weight; 74 c.cm. per kg. of body weight; 8·9 c.cm. per cm. of height); average values for healthy children of the same age (Congo red) being: total volume, 1,535 c.cm. (8·9 per cent. body weight; 84 c.cm. per kg. of body weight (range 76–95 c.cm.); 13 c.cm. per cm. of height (range 11·5–15·5 c.cm.).

Blood transfusion was given on November 19, using bank blood, of which 175 c.cm. had a haemoglobin of 7·01 g. per cent. and 80 c.cm. a haemoglobin of 9·83 g. per cent.

Case 2. J. C., aged two years three months, was admitted on November 6, 1945, with a history of increasing pallor and cervical lymph gland enlargement of three months' duration. The condition proved to be one of aleukaemic lymphatic leukaemia. He was a well-grown child, 109 per cent. of expected weight and 104 per cent. of expected height. Blood investigation on November 7 gave the following figures: Haemoglobin, 3·7 g. per cent.; erythrocytes, 1,210,000 per c.mm.; leucocytes, 8,000 per c.mm.; haematocrit reading, 9·4 per cent.; mean corpuscular volume, 78 c.μ; mean corpuscular haemoglobin concentration, 36 per cent.; mean corpuscular diameter, 7μ; total plasma protein, 7·35 g. per cent.

The total blood volume before the first transfusion (November 7) was 1,147 c.cm. (8·8 per cent. body weight; 84·3 c.cm. per kg. of body weight; 13·2 c.cm. per cm. of height); before the second transfusion (November 21) it was 1,366 c.cm. (10·9 per cent. body weight; 103·5 c.cm. per kg. of body weight; 15·7 c.cm. per cm. of height). The average values for healthy children of the same age group (Congo red) are: total volume, 964 c.cm. (9·3 per cent. body weight; 88 c.cm. per kg. of body weight

(range 86–104 c.cm.); 10·9 c.cm. per cm. of height (range 10–12·5 c.cm.)).

He was transfused on two occasions: (1) November 11,230 c.cm. of bank blood containing 11·6 g. per cent. haemoglobin; (2) November 21, 165 c.cm. of packed red cells, containing 15 g. per cent. haemoglobin.

The haemoglobin values in the above two cases are given in table 1.

TABLE 1

HAEMOGLOBIN VALUES

	Case 1	Case 2	
		1st transf.	2nd transf.
	g. per cent.	g. per cent.	g. per cent.
Before transfusion	3·40	1·70	3·03
5 mins. after ,,	4·42	3·74	6·02
12 hrs. after ,,	3·51	—	—
24 ,, ,,	3·58	4·19	5·70
48 ,, ,,	4·34	—	—
Transfused blood	7·01 (175 c.cm.) +9·83 (80 c.cm.)	11·66 (230 c.cm.)	15 (165 c.cm.)

Estimation of Blood Volume

In determining the blood volume of shocked patients before blood transfusion Hill (1941) made use of the haemoglobin values as follows:

If x = initial blood volume before transfusion
V = volume of blood transfused
Hb_v = haemoglobin concentration of the transfused blood
Hb_1 = haemoglobin concentration before transfusion
Hb_2 = haemoglobin concentration after transfusion,

then, by equating the total quantities of haemoglobin,

$$xHb_1+VHb_v=(x+V)Hb_2.$$

Hence
$$x=\frac{V(Hb_v-Hb_2)}{Hb_2-Hb_1}.$$

In neither of these patients did the initial blood volume (B.V.) calculated from the above formula tally with the observed blood volume determined by the Congo red method at the beginning of the experiment (table 2).

Effect of plasma shifts. McMichael et al. (1943) pointed out that a serious source of error in the above formula was the occurrence of plasma shifts, as the red cell volume in man is constant, apart from the normal removal of effete cells and the addition of new cells from the bone marrow (Ebert and Stead, 1941). The former authors accordingly modified the formula in the following manner. If y c.cm. of plasma leave the blood before the final

TABLE 2

	Case 1	Case 2	
		1st transf.	2nd transf.
	c.cm.	c.cm.	c.cm.
Initial B.V. (Congo red)	843	1,147	1,366
Initial B.V. (Hill):			
Taking Hb_2 at 5 mins.	869	896	496
,, ,, 12 hrs.	10,167	—	—
,, ,, 24 ,,	5,447	690	575
,, ,, 48 ,,	964	—	—

haemoglobin estimation, then, by equating the total amounts of haemoglobin,

$$xHb_1+VHb_v=(x+V-y)Hb_2.$$

Hence
$$x=\frac{V(Hb_v-Hb_2)}{Hb_2-Hb_1}+\frac{yHb_2}{Hb_2-HB_1}$$

If there is a shift of fluid to the circulation during transfusion, then the y fraction becomes a negative quantity. It will be seen, therefore, that if fluid leaves the blood stream before the final haemoglobin estimation, the value for x as calculated by Hill's formula will be too small by the value of the fraction $\frac{yHb_2}{Hb_2-Hb_1}$, while if fluid is added to the circulation x will be too large by the same amount.

From the results shown above, using the original formula of Hill, the following conclusions were drawn:

1. In case 1 no significant fluid shifts took place during the transfusion. The results at 12, 24, and 48 hours, however, are obviously too high, that for 12 hours ridiculously so. Therefore it was assumed that fluid had been added to the circulation in considerable amount following the transfusion.

2. In case 2, in both instances, fluid must have left the blood stream during the actual transfusion. After the first transfusion, fluid continued to leave up till 24 hours, while after the second a small

TABLE 3

	Case 1	Case 2	
		1st transf.	2nd transf.
	c.cm.	c.cm.	c.cm.
Initial B.V.	843	1,147	1,366
Volume transfused ..	255	230	165
Fluid shift :			
During transfusion..	0	−137	−432
0–12 hours after ..	+292	−135	+61
12–24 ,, ,, ..	−61	—	—
24–48 ,, ,, ..	−209	—	—

\+ indicates addition of fluid to the circulation.
− indicates withdrawal of fluid from the circulation.

amount of fluid was added to the circulation during the 24 hours ensuing.

The modified formula was then applied to calculate *y*, the amount of fluid shift, by substituting for *x*, the observed initial blood volume estimated by the dye method. The results shown in table 3 were obtained.

Post-transfusion Response

It is of interest to note the difference in post-transfusion response in these two patients, who were alike in exhibiting a very severe degree of anaemia. Two main points of contrast exist, which may help to explain the difference in reaction.

The initial state of the blood volume differed in the two cases. J. L., the coeliac dwarf with macrocytic anaemia, whose reaction during the first twelve hours was that of fluid addition to the blood, had a blood volume which was rather low when related to weight, but, when related to height, definitely below the average for his age group. As the child was only 53 per cent. of expected weight, in contrast to 86 per cent. of expected height, the height relationship forms a better basis for comparison with healthy children (Gibson and Evans, 1937). J. C., on the other hand, had an initial blood volume which was rather higher than the average—why this is so is not apparent—and the response to transfusion was that of fluid shift to the tissues, the exact opposite of what occurred in case 1. It has been shown that, when the blood volume is at a normal level, transfused serum tends to leave the circulation within one to two hours (Sharpey-Schäfer and Wallace, 1942a). Similarly with transfusion of whole blood in chronic anaemia the added plasma may disappear even during the transfusion, particularly if the rate of giving is slow (Marriott and Kekwick, 1940).

The other factor which may explain these results is the different relationship existing in the two patients between the plasma protein levels of the blood of donor and recipient. If a patient is transfused with blood of a higher protein content than his own there is likely to be a transference of fluid from the tissues to equalize the osmotic pressures, and, conversely, a transfused blood of lower protein content would tend to cause a fluid shift to the tissues (Metcalfe, 1944). Taking an average of 6 g. per cent. as the total protein level of bank blood, it will be seen that J. L. had a plasma protein level well below this (4·35 g. per cent.) and J. C. considerably above (7·35 g. per cent.).

The failure in case 1 to retain the additional fluid after 48 hours may be due to the fact that the added protein was rapidly withdrawn from the circulation to make good the deficiencies in the protein stores, which, considering his state of prolonged malnutrition, were probably low (Chang, 1932; Madden and Whipple, 1940; Ebert et al., 1941; Beattie and Collard, 1942). That some of the fluid removed from the plasma as a result of transfusion may enter the red cells is demonstrated in case 2 (Dyson et al., 1944). The mean corpuscular volume and the mean corpuscular haemoglobin concentration in this case are shown in table 4.

TABLE 4

Date	M.C.V.	M.C.HbC.
	c.μ	per cent.
November 7	78	38
(November 11: transfusion)		
November 21	114	23
(Later same day: transfusion)		
November 28	109	24

In view of the recent work on the increased cardiac output and poor cardiac reserve in chronic anaemia (Sharpey-Schäfer, 1944; Hunter, 1946), and the dangers of transfusion unless by slow drip (Altschule and Gilligan, 1938; Sharpey-Schäfer, 1945), it is interesting to note that in these two patients the blood was syringed into a vein at the rate of about 5 c.cm. per minute, and that neither showed any adverse reaction. Both cases showed such extreme pallor before transfusion, however, that it may be concluded that the compensatory vasoconstriction was well marked. During the transfusion distinct flushing and heat of the skin were noted, but without venous engorgement, indicating that the dilatation of previously constricted vessels had enlarged the vascular bed sufficiently to accommodate the increased blood volume (Sharpey-Schäfer and Wallace, 1942b).

Summary

The difference in the behaviour of the blood volume following transfusion in two severely anaemic children has been studied. In one case fluid was added to the circulation; in the other it was withdrawn.

The suggestion is made that the results can be explained by the difference in the initial blood volume of the two patients, and in the plasma protein levels of the blood of the donor and recipient.

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THE CARE OF PREMATURE INFANTS AT HOME

BY

F. J. W. MILLER, M.D., M.R.C.P., D.C.H.

(From the Department of Child Health, Newcastle-upon-Tyne)

It has long been apparent that an improvement in the care of premature children at home or in hospital would result in a substantial reduction in neonatal infantile mortality rates. In March, 1944, this was given official recognition in the form of a circular sent to Welfare Authorities (Ministry of Health, 1944), with recommendations for the care of premature children at home and in hospital. It was recognized that it might then be impossible for authorities to implement all the recommendations, but they were urged to do what they could. In Newcastle-upon-Tyne the matter had already been under consideration, and we decided first to make the experiment of providing adequate home care in order to have figures as a basis of comparison with institutional care and data for the guidance of future policy. The results of the care of premature infants in special hospital units are well known and have recently been described in detail by Crosse (1945), but the possibilities and the results of home care seem to have received little attention, although Brockington (1944) reported a survival rate of 66 per cent. (62 out of 94 births) for premature children attended by domiciliary midwives in the county of Warwickshire during 1943. The object of this note, therefore, is to give an account of the home care of premature infants in Newcastle-upon-Tyne from January, 1945, to May, 1946. The results will be given, and the equipment provided and the methods used will be described briefly: the special home provision was simple and excluded much that is considered essential in hospital.

TABLE 1

RESULTS OF THE CARE OF ALL PREMATURE INFANTS AT HOME

(Attendance of midwife: one month if necessary)

	Total	Living	Dead	Survived (per cent.)	Premature infant ward survival rates (Crosse, 1945) (per cent.)
Less than 2½ lb.	18	—	18	—	10
2½–3½ lb.	24	7	17	29	50
3½–4½ lb.	40	33	7	82	75
4½–5½ lb.	62	58	4	93	90
Totals	144	98	46	68	65

TABLE 2

RESULTS OF SPECIAL CARE AT HOME

(Under conditions described)

	Total	Living	Dead	Survived (per cent.)	Premature infant ward survival rates (Crosse, 1945) (per cent.)
Less than 2½ lb.	2	—	2	—	10
2½–3½ lb.	10	5	5	50	50
3½–4½ lb.	20	20	—	100	75
4½–5½ lb.	11	11	—	100	90
Totals	43	36	7	83·7	65

Results

During the 17 months from January, 1945, to May, 1946, inclusive, 144 live premature infants were born at home. Of these, 43 received special care from one ' premature ' infant nurse seconded for the purpose from the municipal midwifery service, and the remainder were nursed by the midwife or maternity nurse attending the case. These groups cannot be directly compared, because the cases which received special care were not taken alternately with those which did not, and several factors of selection were present. For example, the ' premature ' nurse was sometimes unable to take more cases; assistance was probably most often needed by families in the poorest circumstances; if the child was either very feeble and likely to die in an hour or two, or very lusty and likely to survive without difficulty, assistance might not be called. For these reasons, therefore, no direct comparison is possible,

but the results of the care of all prematures will be given, and then those who received special care, and each will be compared with the survival rates of premature babies in hospital as given by Crosse (1945). The numbers are small and cover a short period of time, but they are encouraging and there is no doubt that the results of this first period can be improved.

Equipment and Staff

Newcastle-upon-Tyne is an industrial city of 265,000 inhabitants. In the years of economic depression before 1939 the population suffered severely, and housing conditions are still very bad. Domiciliary midwifery is conducted largely by the midwives of the municipal service and the district service of the voluntary hospital, the Princess Mary Maternity Hospital, and the majority of infants are born at home (65 per cent. in 1945). The incidence of prematurity is between 6 and 7 per cent., so that 250–300 premature infants are born each year; of these, approximately 80 to 100 are born at home and the remainder in hospitals or nursing homes. There is accommodation for six premature infants in the Maternity Unit of the Newcastle General Hospital, but this is insufficient to allow the admission of infants from the district, and further accommodation is not possible without new building.

Under these circumstances, and for the reasons given above, it was decided to concentrate upon the care of infants born at home. As a beginning the following provisions were made.

Twelve sets of equipment were placed at the Newcastle General Hospital and made available on request for loan to any householder inadequately provided. Each set comprised draught-proof cot with detachable linings, hot-water bottles, mattresses, blankets, Belcroy feeders, thermometers, etc. Electric blanket pads and oxygen are not included in the equipment; the former because there is a danger of overheating the infant, and the latter because constant skilled administration is required for its use.

All the midwives of the municipal service have been given instruction concerning the care of premature infants, and as soon as staffing difficulties are eased each midwife is to be given a ' refresher ' course, of at least one month, in the Premature Unit at the Newcastle General Hospital. One midwife has been seconded for the whole-time care of premature infants, and one other midwife works half time in this service. The midwife engaged primarily on the care of the infants was chosen because of her interest in the work and her experience of 23 years in midwifery practice; before starting work she was given a period of training in hospital as described above.

It has not yet been possible to arrange for a supply of breast milk for this service, but in practice it is found that the nurse is very often able to obtain milk from the mother and that very small infants are able to breast-feed satisfactorily.

The services of a home help are supplied wherever this is necessary, but it is pleasant to record that the spirit of neighbourliness and the tradition of help within the family are not yet dead in the north of England.

Method of Operation

Any medical practitioner or midwife faced with the care of a premature infant at home may call for assistance by telephoning the maternity hospital, and help is limited only by the availability of equipment and nursing staff. The equipment is sent out by hospital ambulance, which at night also picks up the nurse (during the day she uses her own car). After arrival at the home, the ' premature ' nurse takes over the care of both mother and child, and the original midwife has no further responsibility in the case. The ' premature ' nurse explains to the family why special attention is given to very small children, which particular dangers exist, and how she will require the co-operation of the whole family in order to do her best for the infant. Her personality is such that this co-operation is always forthcoming.

The maximum number of cases which she can care for at any given time is three; the number of visits and the length of each visit are determined by the circumstances of the case and are left to the judgement of the nurse. In some cases she has stayed all night or all day, but as a general rule either a grandmother, a member of the family, or a neighbour performs the duty of sitting with the child at night or whenever necessary during the day. Practically speaking, a maximum of three visits each day is possible: as a routine at least two visits for fourteen days, then one visit each day until the twenty-eighth day has been reached satisfactorily. The longest time the nurse has attended a case has been seven weeks. Before the ' premature ' nurse stops visiting, the district health visitor takes over the supervision of the child so that there is a continuity of help available. This is made very effective by the excellent spirit of co-operation which exists between the midwives and health visitors of Newcastle.

The ' premature ' nurse is also a midwifery teacher and usually has living with her a pupil midwife who accompanies her to her cases and learns her methods of dealing with the infants. The rôle of a ' premature ' nurse is friend, helper, and teacher; the points upon which she concentrates are feeding, warmth, standards of cleanliness, and the avoidance of infection. The results speak for themselves and are, I believe, largely a result of the nurse's personality, which brings out the best qualities of the parents and leaves a sense of accomplishment which is very good for the whole family.

Financial Arrangements

Up to the present time no charge for the loan of equipment and no extra charge beyond the fee payable for the services of a midwife has been made.

The cost to the Authority is about twice that of the services of a midwife, as the ' premature ' nurse is paid as a midwife and looks after half the number of cases when concentrating on the infants as she would do if acting as a domiciliary midwife.

Conclusion

The intention of this note has been to give the experiences of the home care of premature infants in an industrial city over a period of seventeen months. It has been written at this stage because those results have been encouraging enough to make further experience desirable, and because they will bear comparison with those obtained in premature infant units. It is no part of this note to advocate that premature infants should be born at home, but simply to state that if they are born there they should not necessarily be removed to hospital. Ultimately the best results will be obtained when premature births can be avoided or planned to take place under the best conditions.

The extension of this service would appear to be in two stages: first, to provide specialized nursing sufficient for all premature infants born at home; secondly, to train all midwives to be competent to care for these infants, so that any midwife would be able to give specialized care and attention whenever a case occurred in her own practice.

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CASE REPORTS

ACUTE AND CHRONIC GASTRIC ULCERS IN AN INFANT

BY

CHARLES PINCKNEY, M.B., F.R.C.P.

(From the Children's Unit, Sector VII, E.M.S. Hospital, Old Windsor)

(WITH POST-MORTEM REPORT BY A. GORDON SIGNY, M.B., B.S.)

The possible occurrence of peptic ulcers in infancy should be borne in mind when a marasmic infant fails to improve although there is not sufficient evidence of an infection in the gastro-intestinal tract. Franklin (1942) describes well the puzzling gastro-intestinal symptoms in this type of case. Guthrie (1942), in a report on cases with a review of the literature, states that marasmus is the condition most frequently associated with peptic ulcers in infants past the neonatal period.

This case is reported because few have so far been described in this country; Paterson (1922), reporting on two cases, states that in the previous twenty years there was only one case in the literature. In the present case it is of some interest that during the life of the infant peptic ulceration was recognized as being the most probable diagnosis; and treatment to promote healing was instituted without, however, a successful result.

Case report. S. E., a male, aged eight weeks, was admitted to hospital on February 28, 1945. The birth weight was 6 lb. 8oz., and there had been a normal delivery. The child had been breast-fed for two weeks, but this was then discontinued owing to breast abscesses. He was put on a dried milk half cream mixture for one week, but he vomited almost every feed. He was then changed to another brand of half cream dried milk for another week, whereupon he vomited less. However he continued to show malnutrition and loss of weight, so the feed was changed to a sweetened condensed milk; but vomiting continued, and on the day previous to admission some dark blood was present in the vomit.

ADMISSION. On admission the child weighed 5 lb. 15 oz., showing gross wasting but no dehydration. He was put on to half strength Hartmans' solution for twenty-four hours; then sweetened condensed milk was gradually introduced. In the first ten days he had only one day of vomiting, and his weight increased to 6 lb. 4½ oz.

MARCH 3. Twelve days after admission, vomiting became persistent again. Gastric lavage showed a residue of two ounces and some mucus present.

MARCH 7. Vomit became bloodstained, and gastric lavage still showed two ounces residue, with altered blood clot present. The child passed two 'tarry' stools. He was given vitamin K.

MARCH 8. Both ear-drums became pink; bilateral myringotomy was performed, but only blood was obtained.

MARCH 9. Bilateral mastoidectomy was performed, but mucoid fluid only was present in both mastoid processes. After this the child was given intravenous drip transfusion of 5 oz. of blood. The following day he had improved but the stools were still 'tarry.' Vomiting continued, with altered blood still present.

MARCH 11. He became more anaemic, and was given an intravenous blood transfusion of 5½ oz.

MARCH 15. Hb was 104 per cent., but vomiting still continued with altered blood present.

MARCH 26. Hb was 45 per cent., and 20 c.cm. of blood was injected into each buttock, followed on the next day by a further blood transfusion of 5 oz. Bleeding still continued, however, and it appeared now certain that we were dealing with a case of bleeding peptic ulcer. During the whole of this time the weight had very slowly increased, having now reached 7 lb. 2 oz. The feeds had been gradually changed from a sweetened condensed milk to a 2:1 cow's milk mixture with the addition of an ounce of dextrimaltose daily. With the probable diagnosis of a bleeding peptic ulcer, olive oil and kaolin were given before alternate feeds in ½-drachm doses. Intramuscular injections of crude liver extract were also given three times weekly in doses of 0·5 c.cm. With these measures the weight slowly increased to a maximum of 7 lb. 13 oz. on the tenth week of

admission, but the infant never seemed happy and continued to have occasional vomits containing altered blood.

APRIL 4. Hb had dropped to 51 per cent. Wassermann reaction was negative. Kahn negative.

APRIL 9. An intravenous transfusion of 5 oz. of blood was given.

APRIL 27. Hb was 50 per cent.

APRIL 30. A further blood transfusion of 5 oz. was given. During the eleventh and twelfth weeks, however, vomiting of blood increased and stools became more 'tarry.'

MAY 6. The infant collapsed and died.

Investigations

DATE	HB Per cent.	BLOOD TRANSFUSION oz.
March 9	—	5
,, 11	—	5½
,, 15	104	—
,, 20	83	—
,, 26	45	—
,, 27	—	5
April 4	51	—
,, 9	—	5
,, 13	97	—
,, 27	50	—
,, 30	—	5
May 5	54	—

MAY 8. Necropsy was performed by Dr. A. Gordon Signy. The body was that of a male infant fairly well nourished. There was some brownish blood in the mouth and nares and in the oesophagus. The stomach (fig. 1) measured 16 cm. from the cardia to the pylorus. It was filled with brown, altered blood mixed with fresh, partially clotted blood. On the gastric side of the pylorus there was a deep ulcer measuring 3½ cm. by 2 cm. forming a deep crater with a somewhat overhanging edge. This was filled with blood. Half way up the stomach on the lesser curvature there was a large acute ulcer with thin, undermined edges, measuring 20 mm. by 18 mm., which had almost perforated through the muscularis. Immediately adjacent to it towards the cardia there was a small healing ulcer measuring 16 mm. by 8 mm. and a further minute one measuring 4 mm. by 2 mm. The last two had only destroyed the mucosa and had not penetrated deeper. A further healed ulcer was lying between the two large ones and measured 10 mm. by 8 mm. The cardia was free from ulceration. The duodenum, small gut, and ascending colon all contained obvious blood in various stages of alteration. No other abnormality of the gastro-intestinal tract or any other organ was found. Unfortunately permission to examine the brain was not granted.

Histological examination of the mucosa showed a simple ulceration of the mucosa with lymphocytes and a few plasma cells infiltrating the submucosa and muscular layers of the adjacent mucous membrane (figs. 2, 3, and 4, p. 63).

Summary

A case of acute and chronic gastric ulcers occurring in an infant is reported in detail, the interest being that the condition was recognized during the infant's life.

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(*For Illustrations of this Article see page 63*)

ENTEROGENOUS CYSTS OF ILEUM

BY

J. L. PINNIGER, D.M., M.R.C.P.

Lecturer in Pathology, St. Thomas's Hospital Medical School, London

A description is given below of a male infant having enterogenous cysts of the ileum adjacent to the ileocaecal valve. It seems worth while to add this case to those few already described in order to emphasize that enterogenous cysts in this region are a not too rare cause of acute intestinal obstruction in the young, curable by appropriate surgery. In this case the initial symptoms and signs were misleading as to diagnosis, and when those of acute obstruction eventually supervened the child was never in good enough condition for operation.

Case History

A male child, three weeks old, was admitted to hospital on April 21, 1945, on account of the sudden onset of vomiting three days previously. The vomiting had persisted since, and the child was beginning to lose weight. The vomits, which occurred after every feed, were large and moderately forceful. The child had produced two or three normal stools each day up to the time of admission, the last one just before admission being slightly green.

Condition on admission. Examination of the child showed evidence of slight dehydration. No mass or peristalsis could be observed in the abdomen and there were no other abnormal physical signs. The temperature and pulse were normal. A diagnosis of gastro-enteritis was made, and the child was put on to one-third strength Cow and Gate feeds and intermittent subcutaneous saline therapy.

Progress. For the next four weeks the child's condition remained more or less stationary. He continued to vomit up to four times daily and his bowels were opened up to five times. His weight fluctuated between 8 lb. 4 oz. and 8 lb. 11 oz. Towards the end of the period the dehydration became more marked and subcutaneous saline was given more frequently. On one occasion 5 oz. of blood were transfused. In the fifth week deterioration became more rapid, and on May 20 a continuous tibial saline drip was started. The next day the child began to get constipated and the abdomen became very distended. The contours of the bowel loops could be seen and high-pitched bowel sounds auscultated. A rectal examination revealed mucus and faeces only.

On May 23 the bowels ceased to act altogether and the child appeared much worse, copious vomits of bright green curds now welling out of the mouth. The abdominal distension had increased still further, and bowel sounds were very noticeable. An enema was given without effect. Intestinal obstruction had now obviously supervened. Continuous infusion of saline was maintained, and an injection of atropine gr. $\frac{1}{200}$ was given intramuscularly. The next day the child appeared even worse. His abdomen was very tense and the skin reddened over the mid-portion of it. Duodenal suction was started, but owing to the extremely rapid deterioration the child was never fit for operation. He died on the evening of May 25. Over the last thirty-six hours the pulse and respirations were much increased, but the temperature continued approximately normal. The breath sounds were very harsh terminally all over the chest.

Autopsy report. The body was that of an emaciated male infant with transfusion puncture wounds over both tibiae.

ABDOMINAL CAVITY. The abdomen was greatly distended. On opening the peritoneal cavity fibrinous adhesions were found between the loops of the small bowel, and also between the bowel and the anterior abdominal wall. In addition the whole of the small intestine showed considerable distension, purple discolouration, and loss of sheen, these changes being most marked in the right iliac fossa and particularly in the distal twenty-three centimetres of the ileum. A firm mass could be palpated in the position of the ileocaecal valve. The whole of the large bowel was collapsed. There was a small amount of turbid greenish-yellow fluid in the peritoneal cavity.

THE ENTEROGENOUS CYSTS. The ileocaecal region, together with five centimetres of colon and ten of ileum on either side of it, were detached from the rest of the bowel and carefully dissected. The mass was found to be due to a cystic swelling lying in the ileum just proximal to, and in fact partly adjacent to the ileocaecal valve (fig. 1). It caused a slight bulging outwards of the external surface of the ileum just medial to the caecum and ascending colon and anterior to the terminal portion of the mesentery of the small intestine.

The long axis of the cyst, which was the larger of two contiguous cysts (see below), was directed inferiorly and slightly medially. Its general shape was that of a dumb-bell, the long diameter being 3·75 cm. and the maximum transverse diameters 2·0 and 2·5 cm. The diameter of the neck was 1·5 cm. The two portions of the cyst separated by this neck consisted of a larger (two-thirds) part within the wall of the ileum and a smaller (one-third) portion which extended into the lumen of the bowel (fig. 2).

Part of the infero-lateral wall of the latter portion formed part of the superior border of the ileocaecal valve, the cyst projecting further into the cavity of the ileum to come into contact with the diagonally opposite wall. The result was that the valve was completely cut off from the rest of the ileum by the cyst.

The wall of the luminal portion was very thin (0·5 mm.). The external wall of the intramural portion was 2 mm. thick; its lateral aspects were firmly supported by the wall of the ileum. The interior of the cyst was of light grey colour and showed coarse and fine trabeculation on the wall of the intramural part. The lining was in part velvety, in part shiny.

On the infero-lateral aspect of the intramural portion of the above cyst another small slit-like cyst was present, approximately 1 cm. in length and depth and 0·2 cm. in width (fig. 2). The interior was of similar colour and texture to that of the big cyst with which it did not communicate.

The fluid contained within the larger cyst was clear, faintly brown-stained and of low viscosity. Some was removed for analysis before the cyst was fixed in Kaiserling solution. The analysis was kindly carried out by Dr. F. T. G. Prunty, who reported the following findings: *p*H 6·9, total protein 1·13 per cent. with a trace of mucus, sugar 17 mg. per cent., cholesterol 14 mg. per cent., chloride 400 mg. per cent. as NaCl. No evidence of enzyme activity could be detected (cf. Rea, 1940).

Many shallow ulcers were found in the mucous membrane in the ileum for about 30 cm. proximally above the cyst. They had irregular slightly overhanging edges and showed no induration (fig. 1). The vermiform appendix was normal. The liver showed diffuse congestion, and the spleen was rather softer than normal. No gross abnormality was found in other viscera.

THORACIC CAVITY. The lower lobe of the right lung showed extensive collapse. The lower lobe of the left lung contained areas of subpleural collapse. Both lungs otherwise were very congested and somewhat firm. There was no abnormality of the heart or thoracic aorta. The thymus was normal.

Microscopical examination. Sections were cut of the cysts and stained with haematoxylin and eosin, haematoxylin and van Gieson's stain, and with mucicarmine for mucin. A section was also cut of one of the ulcers in the ileum proximal to the cyst.

The larger cyst was completely surrounded by smooth muscle, which was continuous with the circular muscular coat of the ileum. The total thickness of muscle was much greater in this area than in the normal bowel on either side. Where the cyst projected into the lumen of the bowel the muscular covering was very thin; at the points of reflection of the bowel on either side, the muscle reached its maximum thickness, and on the peritoneal aspect its width was intermediate. Strands of fibrous connective tissue occurred irregularly within this muscular coat so that in places the cyst appeared to have a muscularis mucosae. For most of the circumference, however, the mucous membrane of the cyst lay directly on the muscular coat. Over a considerable area of the mucous membrane the epithelium had been shed. Where it remains it was of normal intestinal type. The lining cells were tall columnar with clear cytoplasm and basal nuclei. Here and there goblet cells were present. Both these, and many of the lining mucosal cells, stained positively for mucin (fig. 3). The lamina propria was shallow and hypocellular, and contained simple, slightly tortuous tubular glands having epithelium similar to the lining mucosa.

The mucosa of the smaller cyst lying alongside the larger was similar to that of the latter. For about two-thirds of the circumference fibrous connective tissue divided the muscular coat so that the cyst appeared to have a muscularis mucosae over this area (fig. 4).

Section of the ulcer of the ileum showed that it had penetrated as far as the inner aspect of the circular coat, the base being formed by an exudate consisting of lymphocytes with a few neutrophils and eosinophils. The surrounding tissues were congested and oedematous, and showed infiltration with similar inflammatory cells. There was no evidence of a tuberculous infection.

Other histological changes. The lungs showed congestion, oedema, acute bronchiolitis, bronchopneumonia, emphysema, and subpleural collapse. There was severe venous congestion of the liver.

Comment

The cysts described in this case are examples of those broadly known as enterogenous (Evans, 1929) and are almost certainly congenital, the results of aberration of normal development of the intestinal canal. Well over fifty cases having these enterogenous cysts have been reported since the original one of Fraenkel in 1882. They have been shown to exist in many situations, for example, in the wall of the alimentary tract or attached to it or separate from it, in the latter case being usually in the folds of the mesentery. Over 50 per cent. of the reported cysts have been in the region of the ileocaecal valve, though the number in the same position in the ileum, as in this case, is, of course, considerably smaller. Analyses of the case reports and discussion of the modes of development of these cysts have been given more than once (Evans, 1929; Drennen, 1931; Hughes-Jones, 1934; Pachman, 1939), and nothing is to be gained by going into these subjects again.

The cysts described here are like the majority in this region in being intramural (Pachman, 1939). It has been claimed by Dockerty et al. (1939) that such cysts show a faithful reproduction of the layers of the intestinal wall, but this certainly

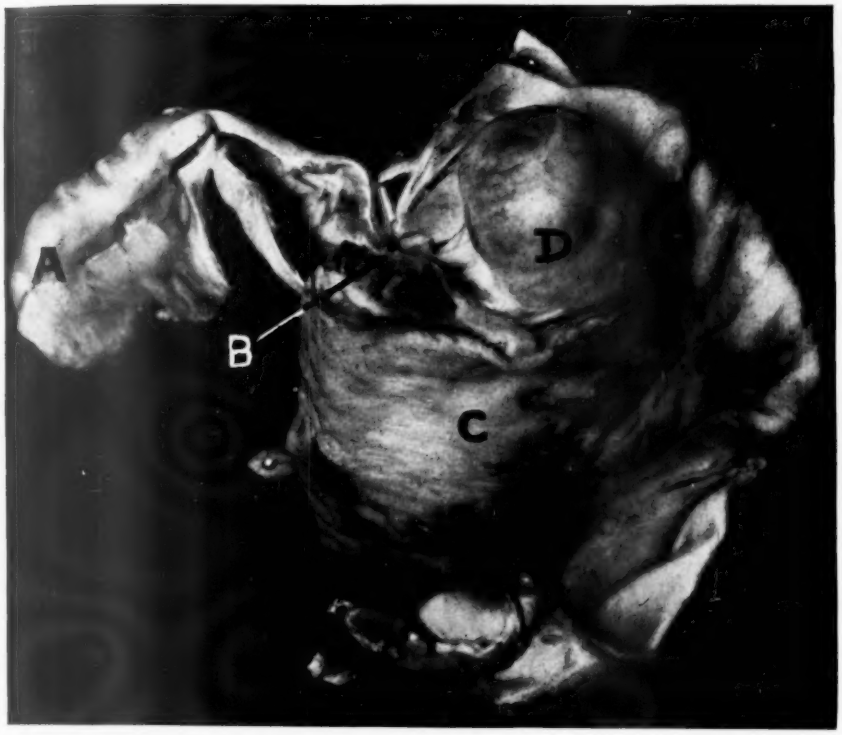

FIG. 1.—(A) colon; (B) ileocaecal valve; (C) ileum showing ulcers on mucosa; (D) cystic swelling.

does not always appear to be so. In the present example the mucous membrane of the larger cyst very frequently lies on the muscular coat without the suspicion of muscularis mucosae or submucosa, and indeed the same state of affairs seems to be shown in the microphotograph of the cyst reported by the authors above. Their case appears from their description and illustrations to be very similar in situation and structure to the one here described.

The extreme thinness of the larger cyst wall where it is covered by the mucous membrane of the ileum, the dumb-bell shape of the cyst, and the comparatively recent onset of the acute intestinal obstruction, suggest that the cyst had enlarged inwards to occlude the lumen of the ileum relatively quickly towards the end. Presumably the starting of feeding soon after birth would have caused an increase in the secretory activity of the cyst epithelium, and it would be when the intra-cystic pressure became greater than the containing pressure of the weakest portion of the wall that the most rapid dilatation of that section of the cyst took place. The presence of mucus-secreting cells in the epithelium and mucin in the fluid gave evidence that the epithelium was secreting actively at the time of death.

If any symptoms are produced by cysts in the ileocaecal angle, they are usually, as here, those of intestinal obstruction, and they most frequently appear in the first few months of life. Intussusception occasionally results. Resection of a portion of the bowel to include the cyst is the operation most frequently used, and a high proportion of successes has thereby been reported (Pachman, 1939). In this case, it was misleading and unfortunate that a phase simulating gastro-enteritis occurred four weeks before definite signs of obstruction ensued. The child's general condition was thus weakened and, as has already been stated, when the acute obstruction supervened the progress downhill was so rapid that operation could not at that time be entertained.

Summary

A clinical and pathological description is given of two enterogenous cysts occurring in the terminal ileum of a male infant. The child died from intestinal obstruction resulting from the expansion of one of them into the lumen of the ileum. Some features of such cysts are briefly discussed.

My thanks are due to Dr. J. Forest Smith for permission to publish this case, and to Mr. A. E. Clark for help with the photographs.

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(*For Figs. 2, 3, and 4 of this Article see next page*)

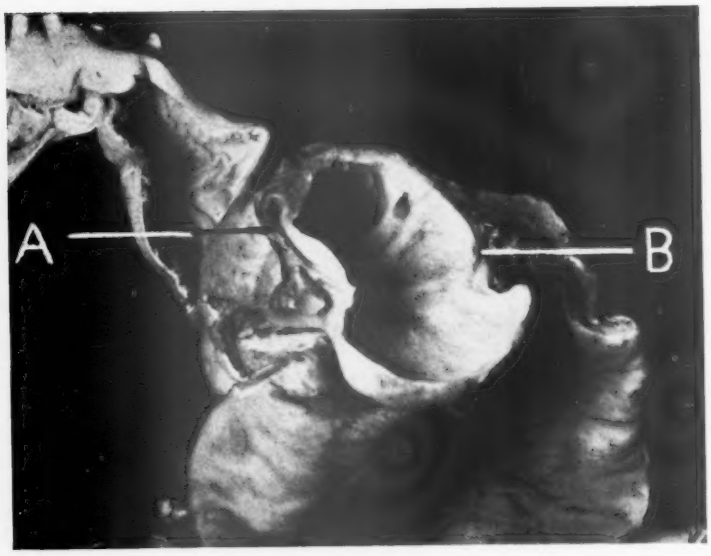

FIG. 2.—(A) smaller cyst; (B) larger cyst.

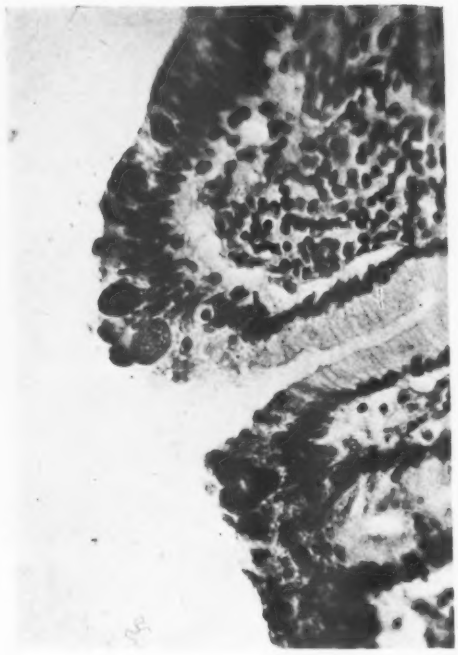

FIG. 3.—Part of the lining epithelium of the larger cyst stained with mucicarmine, showing positive reaction in some of the cells. (× 215.)

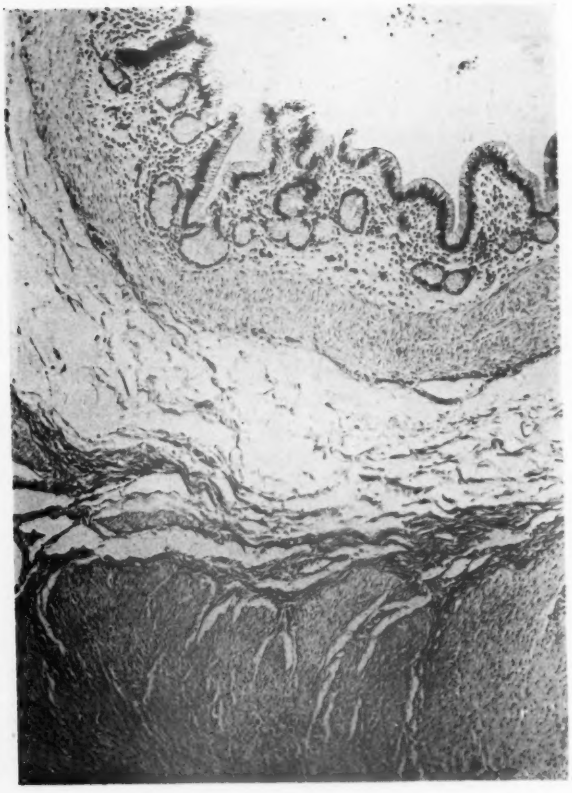

FIG. 4.—Part of the wall of the smaller cyst. (× 45.)

FIG. 1.—Posterior of gastric mucosa, showing two large active ulcers and two healing and scarred ulcers. (Natural size.)

FIG. 2.

FIG. 3.

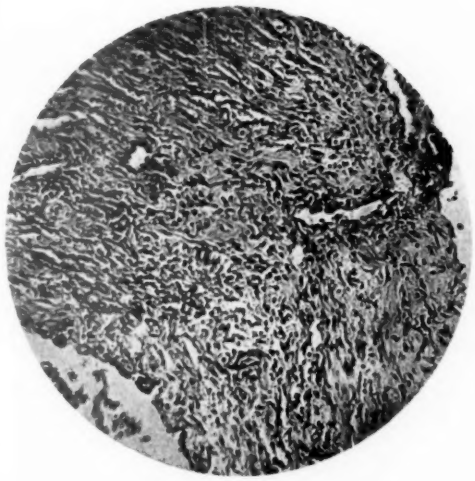

FIG. 4.

FIG. 2.—Low-power microphotograph showing normal mucosa and edge of acute ulcer. (× 30.)

FIG. 3.—High-power microphotograph of A, showing small-celled infiltration of the submucosa and the muscle layer. (× 90.)

FIG. 4.—High-power microphotograph of B, showing fibrous tissue and small-celled infiltration of the ulcer base. (× 90.)

REVIEWS

The Nervous Child. By HECTOR CHARLES CAMERON, M.A., M.D., F.R.C.P., Consulting Physician to the Children's Department, Guy's Hospital. London, Oxford Medical Publications. Fifth edition, 1946. Pp. 252. (Price 10*s.* 6*d.*)

As this has long been a classic, little more need be said than that the fifth edition differs only slightly from the last. The author has added particulars relating to umbilical colic, depth of sleep in enuresis, night terrors, and habitual vomiting of infancy. It must be rare indeed for a medical monograph to contain so much that is as true in 1947 as when it was written in 1919. Like *Tristram Shandy*, *The Nervous Child* should be read regularly; appetite will increase with eating.

The Purpose of the Family: A Guide to the Care of Children. By J. C. SPENCE, M.D., F.R.C.P., Nuffield Professor of Child Health in the University of Durham. The Convocation Lecture, 1946, of the National Children's Home, Highbury Park, London. Pp. 68. (Price 2*s.* 6*d.*)

As would be expected, this book is philosophical, stimulating, and occasionally provocative, and contains a wealth of common sense. It might well be called 'The Mother's Charter,' for seldom has her cause been more eloquently pleaded. It has become fashionable to blame the mother for having too few children, for relapsing into slutdom when she has too many children, for neglecting her children, for fussing her children, or for failing to breast-feed her children, and in general to visit the sins of the children on their female parent. There is something refreshingly sane and Victorian in Prof. Spence's view that the maternal instinct is something real and invaluable, built up through the experience of physical and emotional changes accompanying pregnancy, delivery, and lactation, and finally fulfilled through the handling of a family of children of different ages. He even goes so far as to uphold that the mother should be given the opportunity of nursing her sick child in hospital, and be allowed some of the credit for its recovery. That the future of child welfare should come to lie more and more in the hands of spinsters and civil servants, of whom an increasing number have never experienced membership of a large family, is a state of affairs which he rightly deplores. The author even has a kind word for the father, and assigns him a definite, if less important, rôle in the fostering of young children.

Although this lecture was delivered to a lay audience, it should be read by every paediatrician and child psychologist. The National Children's Home is to be congratulated on the choice of the first Convocation Lecturer, and on the decision to publish his lecture and make it available to a wider public.

The Embryology of Behaviour: The Beginnings of the Human Mind. By ARNOLD GESELL, M.D., Ph.D., Sc.D. In collaboration with CATHERINE S. AMATRUDA, M.D. London: Hamish Hamilton Medical Books. 1946. Pp. 775, 391 illustrations. (Price 21*s.*)

If the reader is prepared to accept the hypothesis that the premature baby can reasonably be described as a 'foetal infant,' he may feel that the title of this book is justified. If, on the other hand, he considers that the behaviour-development of the premature child is likely to be profoundly modified by spending the weeks preceding its expected birthday in the outside world instead of in the uterus, he is unlikely to accept Dr. Gesell's somewhat slipshod commentary on 'the beginnings of the human mind.' In either case, this book contains some interesting photographic and other studies of premature babies of varying degrees of immaturity, is pleasingly produced, and should have a satisfactory sale amongst the senior author's large circle of fans.

Pulmonary Tuberculosis: A Handbook for Students and Practitioners. By R. Y. KEERS, M.D., F.R.F.P.S., and B. G. RIGDEN, M.R.C.S., L.R.C.P. With a Foreword by F. H. Young, O.B.E., M.D., F.R.C.P. Edinburgh, E. and S. Livingstone, Ltd. Second edition, 1946. Pp. 277. Profusely illustrated. (Price 17*s.* 6*d.*)

The paediatrician, who is likely to measure this book with his own yardstick, will be disappointed to find that neither 'infancy' nor 'childhood' appears in the index, and that there is no chapter devoted specifically to tuberculosis in early life. There is a brief discussion of the age-incidence of pulmonary infection, a reference to the use of B.C.G., and figures are given relating to various large-scale studies of positive tuberculin-reactors. The impression is gained, however, that the practitioner or student who obtained his information from this source would be left without any adequate idea of the importance of childhood tuberculosis as a cause of ill-health, and with little guidance as to how the individual child should be handled. Apart from these serious criticisms the book can be recommended as clearly written and containing a great deal of useful information in small compass; the fact that it has gone into a second edition a year after the publication of the first shows that it meets a real need. The production is excellent, and the many radiographs well reproduced.